federal register

FRIDAY, DECEMBER 22, 1978
PART VI

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

■

RECOMBINANT DNA RESEARCH

Revised Guidelines

[4110-08-M]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

National Institutes of Health

RECOMBINANT DNA RESEARCH

Revised Guidelines

I am announcing today several actions affecting the conduct of recombinant DNA research in this country.

In taking these steps, I have been guided by my responsibility to allow the maximum freedom of scientific inquiry consistent with the protection of the public health and the environment and with respect for the important ethical concerns surrounding genetic research in general.

The research techniques used to produce recombined molecules of deoxyribonucleic acid, the complex chemical that codes genetic information for all living cells, hold great promise for significantly advancing our understanding of fundamental biological processes. Moreover, this research may also hold potential for the commercial production of needed biological materials and agricultural products.

From the pioneering days of this research, many of this nation's leading scientists expressed concern that the insertion of foreign genes into microorganisms could carry the potential for harm by yielding new disease-producing organisms. Although no harm has resulted from recombinant DNA research to date, there has been widespread uncertainty as to the degree of risk involved.

We must always recognize that scientific knowledge is not immutable; it is constantly changing as research generates additional information and understanding. Public policy in the field of science must therefore be flexible—to allow change as knowledge and understanding increase. The requirements that we impose must constantly be revised and updated to reflect new knowledge. Today the experience and insights that we have gained provide the basis for relaxing some of the restrictions the National Institutes of Health first imposed in 1976 on recombinant DNA research it funds.

The actions I am announcing today strive to allow the greatest freedom of scientific inquiry possible. At the same time, they provide the protections necessary to safeguard the public health and environment and also provide the opportunity for those concerned to raise any ethical issues posed by recombinant DNA research.

Specifically, I am today:

- Approving final guidelines prepared by the National Institutes of Health that significantly revise the safety requirements for conducting recombinant DNA research;
- Taking immediate steps to require that research conducted by private companies complies with the NIH guidelines, primarily through use of the regulatory authority of the Food and Drug Administration (at Appendix A);
- Requesting the Environmental Protection Agency to review its authority and to take all action it can to require compliance with the NIH guidelines by companies that carry out DNA research but whose products are not regulated by the Food and Drug Administration;
- Directing NIH to increase its research designed to determine the extent of risk associated with recombinant DNA research (at Appendix B);
- Broadening substantially the public representation on the HEW advisory committee that will assist NIH in administering the revised guidelines;
- Increasing significantly public access to information about recombinant DNA research activities and increasing public participation in the administration of the guidelines in local communities.

Revised Guidelines

The revised final guidelines that NIH has developed and that I am approving today set new directions for regulation of future recombinant DNA research. These final guidelines retain much of the guidelines that NIH published in proposed form last July. But NIH has made many revisions based on public comment and on the review conducted by a Departmental committee. The Director, NIH, has prepared a Decision Document responding to the public comments and explaining the reasons for the revision.

The final guidelines relax some of the restrictions under which recombinant DNA research has been conducted since 1976, and at the same time increase the role of the public in approving and monitoring recombinant DNA experiments.

In particular, these final guidelines relax in two major respects the guidelines that were placed in effect in 1976.

- *The revisions exempt altogether five categories of experiments from the guidelines' restrictions.* NIH has concluded that these experiments present no known health risk. Approximately one-third of research covered under the existing guidelines would be exempted under the revised standards.

The revised guidelines continue to ban all six categories of potentially hazardous research that the 1976 guidelines prohibited. They will now, however, permit the Director of NIH to grant—following public notice and comment—case-by-case exceptions to these prohibitions with appropriate safeguards.

- *The revised guidelines will ease restrictions on other permissible experiments.* Depending on the potential risk of an experiment, both the 1976 guidelines and today's revised guidelines require a researcher to comply with one of four levels of protective laboratory procedures and one of three levels of restrictions on the type of organism that may be used in the research. The revised guidelines assign almost all categories of research physical containment and/or biological containment levels at least one step lower than in the 1976 guidelines. Since the likelihood of harm now appears more remote than was once anticipated, the scientific community has now concluded that this downgrading is appropriate. The four levels of physical containment and three levels of "biological containment"—the use of weakened organisms that cannot survive outside the laboratory—set by the 1976 guidelines would remain the same.

Based on the review and public hearing conducted by a Departmental committee, the guidelines have been significantly rewritten from the July version to increase public participation at both the local and national level:

- *Twenty percent of the members of local Institutional Biosafety Committees (IBC's) must represent the general public, and have no connection to the institution.* The 1976 guidelines had no such requirements for public participation.
- *Important records must be made public.* The bulk of IBC records must be made available to the public and problems, violations, illnesses and accidents must be reported to NIH.
- *At the national level, major actions cannot be taken without advice of the Recombinant DNA Advisory Committee (RAC) with public and Federal agency comment.* Major actions include decisions to approve on a case-by-case basis experiments that are generally prohibited, to exempt additional categories of research from the guidelines, to permit the insertion of genes in new types of bacteria, and to approve changes in the guidelines themselves.

Finally, today's revised guidelines provide more explicit guidance both for local institutions and for NIH to follow in implementing the guidelines.

- Institutions must develop emergency plans covering accidental spills and personnel contamination; health surveillance programs for projects needing such safeguards; and training programs for IBC members, researchers, and other laboratory staff.
- Under the revised guidelines, the NIH Director cannot approve pro-

posed actions unless he determines that they present no significant risk to health or the environment.

GUIDELINE COVERAGE

The revised guidelines apply to *all* recombinant DNA research conducted at any institution which receives NIH funds for recombinant DNA research. At these institutions, even research conducted without NIH support must comply with the guidelines. Other research agencies of the Federal government have assured us that they will require compliance with the NIH guidelines for all recombinant DNA research that they conduct or support.

We are also taking action to assure that the guidelines apply, to the greatest extent possible, to research conducted in the private sector.

● At my direction, the Food and Drug Administration is today announcing its intent to propose than any recombinant DNA research submitted to satisfy FDA's regulatory requirements must have been conducted in compliance with the NIH guidelines.

● I have also written to Douglas Costle, the Administrator of the Environmental Protection Agency (EPA) and asked him to review EPA's regulatory authority to determine whether EPA can regulate recombinant DNA research conducted privately that is not submitted to the FDA. I have asked him to take all action he can.

If both FDA and EPA act to regulate privately conducted recombinant DNA research, virtually all recombinant DNA research in this country would be brought under the requirements of the revised guidelines.

BROADENED COMMITTEE MEMBERSHIP

I will announce shortly the names of 14 new members of HEW's recombinant DNA Advisory Committee. In addition to scientists who are experts in molecular biology and other disciplines, the Committee will be expanded to include persons knowledgeable in a wide variety of fields such as law, public policy, ethics, the environment and public health. The Committee will serve as the principal advisory body to the Director of NIH and to the Secretary of HEW on recombinant DNA policy.

INCREASED RISK ASSESSMENT RESEARCH

While our knowledge about the risks of recombinant DNA has increased dramatically, much remains unknown. The scientific community must continue to assess the extent of the risks posed by recombinant DNA research. I am therefore directing the Assistant Secretary for Health and the Director of the National Institutes of Health to formulate a plan for carrying out a balanced program of additional risk assessment experiments. In my view, the more risk assessment experiments NIH conducts or supports, the better we can judge whether the guidelines—and actions taken under them—afford appropriate protection for health and the environment.

Today's action represents the culmination of a long and thorough process that has sought at each step to balance the important concerns involved in recombinant DNA research. The National Institutes of Health in 1976 published guidelines to govern research which it funds.

The 1976 guidelines:

● Prohibited six categories of recombinant DNA experiments which experts felt posed significant hazards.

● Defined degrees of physical and biological containment necessary to prevent recombinant DNA organisms from escaping into the environment and surviving.

● Described permissible categories of recombinant DNA research and assigned levels of physical and biological containment for each.

● Described specific roles and responsibilities for principal investigators, research institutions, institutional biohazard committees, and the NIH.

Since issuance of the 1976 guidelines, recombinant DNA techniques have become much more widely used in research, and more has been learned about the limits of potential risks in using this technology.

In light of this new knowledge, the Director, NIH, on July 28, 1978 proposed substantial modification and relaxation of the guidelines. At that time, I named a Departmental review committee consisting of Peter Libassi, the Department's General Counsel, as Chairperson; Dr. Donald Fredrickson, the Director of NIH, as Vice Chairperson; Dr. Julius Richmond, Assistant Secretary for Health; and Dr. Henry Aaron, then Assistant Secretary for Planning and Evaluation. I asked the Committee to examine the proposed guidelines and to hold a public hearing on the guidelines.

In reviewing the guidelines, the committee solicited and heard comments from representatives of environmental groups, unions, pharmaceutical companies, institutional biosafety committees and Congressional staff members. The committee reviewed more than 170 letters from the public commenting on the revisions. The committee planed a vital role in the process which led to the revised guidelines and unanimously recommended that the revised guidelines be approved.

These revised guidelines provide for a flexible, open system that can accommodate new scientific information that may warrant change, either to relax or to increase safety requirements.

I applaud all who have labored to develop these guidelines: The scientific community, the public, and workers at the Federal, State and local levels. This research holds promise for adding to our understanding about basic biological processes. These guidelines should permit that promise to be realized without presenting any significant risk to public health or the environment.

Dated: December 15, 1978.

JOSEPH A. CALIFANO, Jr.,
Secretary.

APPENDIX A

THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE,
Washington, D.C. 20201.

DECEMBER 15, 1978.

MEMORANDUM TO: Commissioner of Food and Drugs, Director, National Institutes of Health.

THROUGH: Assistant Secretary for Health.

SUBJECT: FDA Requirements for Compliance with the NIH Guidelines for Recombinant DNA Research.

With my approval and that of the Assistant Secretary for Health, the Director of the National Institutes of Health is issuing today revised Guidelines for Recombinant DNA Research.

These Guidelines set down requirements for all recombinant DNA research either conducted by NIH or conducted by institutions receiving NIH funds for recombinant DNA research. Other Federal agencies funding recombinant DNA research have agreed to require recipients of their funds to comply with these Guidelines as well.

To the maximum extent possible, we should extend the coverage of the NIH Guidelines to recombinant DNA research carried out in the private sector, with appropriate protection for proprietary and patent rights.

As we discussed, the pharmaceutical industry does most of the recombinant DNA research that is carried out privately in this country. Accordingly, the Food and Drug Administration is issuing today a Notice of Intent to propose regulations. These proposed regulations would require that all recombinant DNA research submitted to the FDA to satisfy the FDA's regulatory requirements be carried out in compliance with the Guidelines. This requirement should bring under the Guidelines the vast majority of recombinant DNA research conducted in this country by the private sector. If FDA does adopt such regulations, there must be close cooperation between NIH and FDA in implementing them. With the Commissioner of Food and Drug taking the lead, you should prepare a plan of action on the steps necessary to apply the Guidelines to the private sector.

Please submit a memorandum describing your proposed plan of action at the time you submit proposed regulations.

JOSEPH A. CALIFANO, Jr.

APPENDIX B

THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE,
Washington, D.C. 20201.

DECEMBER 15, 1978.

MEMORANDUM TO: Assistant Secretary for Health, Director, National Institutes, National Institutes of Health.

SUBJECT: Assessing the Risk of Recombinant DNA Research.

With the issuance today of revised Guidelines for recombinant DNA research, the responsibility of the National Institutes of Health to conduct and support experiments designed to determine the risks of recombinant DNA research becomes even more important than it has been in the past. The revised Guidelines now require a finding by the Director of NIH that each proposed action under the Guidelines "presents no significant risk to health or the environment." It is critical that these judgments, to the maximum extent possible, be based on the firm foundation of documented research that is subject to peer review.

Experience and knowledge gained from the broad range of recombinant DNA research already underway will provide much information for assessing risks. But in many areas special research and careful attention will be needed. To discharge our responsibility to assess risk before certain research is conducted on a wide-spread basis, NIH should formulate a plan for carrying out a balanced program of more such risk-assessment experiments either at NIH directly or under NIH-supported grants or contracts. In my view, the more risk assessment experiments NIH carries out, the better we will be able to judge whether the Guidelines—and actions taken under them—afford appropriate protection for health and the environment.

Your overall plan to conduct risk assessment experiments should be published for public comment and presented for review to the Recombinant DNA Advisory Committee annually. The first such plan should be ready for publication and submission to the Advisory Committee by March 30, 1979.

JOSEPH A. CALIFANO, Jr.

NOTICE OF RELEASE OF REVISED NIH GUIDELINES FOR RECOMBINANT DNA RESEARCH

Today, the Director, National Institutes of Health, with the approval of the Assistant Secretary for Health and the Secretary of Health, Education, and Welfare, is authorizing the release of revised *NIH Guidelines for Research Involving Recombinant DNA Molecules.* The *Guidelines* and a *Decision* of the NIH Director to issue the revised guidelines are published below.

Dated: December 15, 1978.

DONALD S. FREDRICKSON,
Director,
National Institutes of Health.

DECISION OF THE DIRECTOR, NATIONAL INSTITUTES OF HEALTH, TO ISSUE REVISED GUIDELINES FOR RECOMBINANT DNA RESERACH

DECEMBER 1978.

CONTENTS

I. Scope of the Guidelines.
General Applicability.
Prohibitions and Exemptions—General comments.
Prohibitions—Specific Comments.
Exemptions—Specific Comments.
II. Containment.
Physical Containment.
Shipment.
Biological Containment.
Flexibility in Choosing Physical and Biological Containment Levels.
III. Containment Guidelines for Covered Experiments.
General Considerations.
Risk Assessment.
Specific Concerns.
IV. Roles and Responsibilities.
Of the Institution (General).
Of the Institution (Special).
Of NIH (General).
Of NIH (Specific).
V. Footnotes and References.
Appendix A (Director's Decision concerning Appendix A of the Guidelines).
Appendix B (Director's Decision concerning Appendix B of the Guidelines).

APPENDICES

I. Environmental Impact Assessment.
II. Federal Interagency Advisory Committee (list of members).
III. Exchange of letters between Senators and Secretary Califano.

I. SCOPE OF THE GUIDELINES

A number of commentators at the September 15 hearing and correspondents addressed issues concerning the scope of the Guidelines. Views were expressed for an against exempting experiments from the Guidelines even though some argued that the risk was minimal or nonexistent. Specific issues that were raised are discussed below.

GENERAL APPLICABILITY

Several commentators spoke to the scope of the applicability of the Guidelines. Some questioned the right of NIH to apply the Guidelines to investigations not supported by NIH at an institution that receives some NIH funding for recombinant DNA research. Others, however, urged that the scope be broadened to include all institutions receiving NIH or, indeed, DHEW funding for whatever purpose.

I addressed these concerns in my Decision accompanying the proposed revision published in the FEDERAL REGISTER on July 28, 1978. I noted that partial adherence to the Guidelines within an institution would defeat the purpose of extending maximal protection to the community. Thus, it would be inconsistent for NIH to provide funds for recombinant DNA activities to an institution that did not meet the standards of the Guidelines in all of its recombinant DNA research, regardless of the source of funding. This principle is sound and NIH has the authority to apply it.

Some commentators took exception to the statement in the section on General Applicability that once certain research is approved at the local level, it may proceed. Several correspondents pointed out that the language conveys the sense that all recombinant DNA research can proceed solely on the basis of local approval. This is not the case and this section does not, in fact, deal appropriately with the matter. Accordingly, the topic has been deleted from the Applicability section and dealt with extensively in part IV of the Guidelines and in the Administrative Practices Supplement.

Another commentator urged that the requirements of the Guidelines be extended to NIH-supported research in foreign countries. The proposed revised Guidelines (PRG) state that the Guidelines are applicable, but if the host country has rules for the conduct of recombinant DNA projects, then a certificate of compliance with those rules may be submitted to NIH in lieu of compliance with the NIH Guidelines, so long as the safety practices of the two are reasonably consistent. Of course, in countries with no guidelines, the NIH Guidelines must apply to NIH-supported research.

PROHIBITIONS AND EXEMPTIONS—GENERAL COMMENTS

There were a large number of comments on prohibitions, exceptions to prohibitions, and exemptions from the Guidelines. There was some confusion on the difference between exceptions and exemptions. Experiments excepted from the prohibitions are assigned appropriate containment levels and thus must be conducted in compliance with the Guidelines. For experiments under the exemptions (and not affected by prohibitions), the Guidelines do not apply at all.

Several of the commentators spoke to one or more of the criteria used for exempting experiments from the Guidelines. Some said that the criterion for granting exemptions should be safety and not whether DNA exchange occurs in nature. This issue is discussed in the Environmental Impact Assessment accompanying the revised Guidelines in the FEDERAL REGISTER of July 28, 1978.

It was noted there that, according to some commentators, safety rather than "novelty" should be the criterion for exclusion. That is, any recombinant molecule that poses a potential threat to the public health or the environment should be covered by the Guidelines regardless of whether the molecule is a novel one. An opposing view, expressed by other commentators, was that a proper criterion should be whether the potential hazard of the recombinant molecule would differ significantly from the biohazard posed by a molecule already found in nature or from a biohazard that can be successfully handled by conventional methods. It proved impossible to reconcile these differences of opinion in the definition itself, and

so the Exemptions sections was developed.

In my view, the criteria given in the exemptions and prohibitions sections of the PRG defining recombinations similar to natural events are both conservative and reasonable. It should be noted that the wording of prohibition I-D-5, "that are not known to acquire it naturally," is identical to that of the original 1976 Guidelines.

PROHIBITIONS—SPECIFIC COMMENTS

Several commentators requested clarification of prohibition I-D-2 concerning the deliberate formation of potent toxins. Was it intended to cover only toxins for vertebrates or those for all species? A commentator noted that fungi produce antibiotics that are potent toxins for bacteria. It is not the intent of this prohibition to cover such toxins but only potent toxins for vertebrates. Accordingly, new language makes it clear that "potent toxins" refers specifically to vertebrates.

A number of commentators form the agricultural community urged that mechanisms be set in place for waiver of prohibition I-D-4, which bans deliberate release into the environment of any organism containing recombinant DNA. Recognizing the need expressed by these commentators for more definitive standards for allowing exceptions, I will refer the matter to the Recombinant Advisory Committee (RAC) for its consideration. Indeed, in response to several suggestions from commentators, the RAC will be asked to address conditions under which exceptions to various prohibited categories of experiments may be granted.

Another commentator urged that for waiver of the prohibition on deliberate release into the environment, the Guidelines explicitly require compliance with the National Environmental Policy Act (NEPA) and any additional safeguards to be stipulated by EPA. Others urged that full Environmental Impact Statements be filed on most exceptions to the prohibitions. As I noted in my Decision accompanying the PRG on July 28, 1978, all waiver decisions will include a careful consideration of the potential environmental impact. Some decisions may be accompanied by a formal assessment or statement—a determination, however, that can only be made on a case-by-case basis. In the new procedures for the Federal agencies under the Guidelines, all agencies represented on the Federal Interagency Committee, including EPA and OSHA, will have nonvoting members on the RAC, and will thus have opportunity to participate in all the RAC's deliberations. In addition, the Federal Interagency Committee may be convened to discuss issues its members believe are important prior to the granting of any waiver. Exceptions to prohibitions also fall under the procedure described in Section IV-E-1-b-(1) of the Guidelines that involves at least 30 days of public comment.

The standard for exceptions to prohibitions in the Guidelines was a source of much comment. Some commentators believe that the standard should be "no significant risk and a clear social benefit to be realized." Others urged that exception to the prohibitions be justified only to permit special risk-assessment experiments. I believe that Section IV-E-1-b sets the appropriate standard at this time. This is particularly so in light of the new procedural protections described in part IV requiring public and Federal agency participation in such decisions.

There were a number of comments from the private sector concerning the prohibition on large-scale experiments (I-D-6). They noted that the necessity for conducting scale-up experiments (greater than 10-liter volumes) is imminent, and that, in their view, such experiments present no unusual hazards. I recognize the need for conducting experiments with more than 10 liters of culture and the extensive experience of industry in dealing with larger volumes. The criteria set forth in the Guidelines make the prohibition inapplicable when the recombinant DNAs are rigorously characterized and free of harmful DNA sequences. An exception to the prohibition may also be granted [see Guidelines, Section IV-E-1-b-(1)-(e)] and the RAC will begin to consider specific standards for exceptions.

EXEMPTIONS—SPECIFIC COMMENTS

In the PRG all of the prohibitions overrode the exemptions. There were suggestions that certain prohibitions not apply to the exemptions. It was recommended, for example, that the prohibitions relating to the deliberate release of recombinants into the environment and the deliberate transfer of drug resistance not apply to exempt experiments. In my view these prohibitions must continue to apply for the present.

It was also argued that the prohibition on large-scale experiments should not apply to exempt experiments. This prohibition, indeed, is different from the other five, as is explicitly noted in the 1976 Guidelines. In the PRG the language was tightened: "recombinant DNAs known to make harmful products" was changed to "unless the recombinant DNAs are rigorously characterized and are shown to be free of harmful genes." For experiments in the exempt category that call for more than 10 liters of culture, it seems unnecessary to have the recombinant DNAs meet these criteria. Therefore, a fixed prohibition, unduly restrictive in these cases, no longer applies, and experiments which meet the criteria of the exemptions may be conducted in volumes of over 10 liters. The first five prohibitions continue to apply to all experiments and override the exemptions.

A correspondent stated that the inclusion of specific exemptions in the Guidelines is premature. It was recommended that exemptions be granted instead on a case-by-case basis after risk-assessment, NEPA compliance, public participation, and a finding based on experimental data that the exemption presents no significant risk to health or the environment. In my view the five classes of exemption listed in the PRG, as discussed in the accompanying Decision Document and Environmental Impact Assessment, are warranted. It is a view shared by the RAC and many commentators throughout this long period of proposed Guideline revision. All of the participants and observers concerned with the Guidelines will benefit from disengagement of the least potentially hazardous use of recombinant DNA techniques, so that attention may be focused on the areas still encompassed by the Guidelines.

A witness at the September 15 hearing objected to exemption of experiments involving naked DNA, maintaining that the Rowe-Martin experiment showed that the ingestion of naked polyoma DNA by mice resulted in infection. This is incorrect. In that experiment the DNA caused infection in mice only when injected, and then with much reduced ability as compared with the whole virus. It is a common experience that naked DNA molecules are fragile and difficult to retain intact in the laboratory. Ingested DNA would be destroyed in the alimentary tract by stomach acid and the various enzymes that degrade DNA. The one route whereby naked DNA molecules might be hazardous is accidental injection, as into a laboratory worker, The same could be said for many of the chemicals used in experiments. For this reason, the use of hypodermic needles in laboratory procedures is avoided whenever possible. Their use is specifically discouraged in the section of the Guidelines on Containment. Further, Footnote 5 has now been expanded to recommend inactivation of DNA before disposal, and specifically refers to the Laboratory Safety Monograph as a source of advice on acceptable methods.

A commentator on behalf of the RAC's Working Group on Prokaryotic Host-Vectors Other than *E. Coli* K-12 proposed modification of Exemption I-E-3. He provided the following justification: "Addition of the proposed clause ['or which have been trans-

ferred to another host by known physiologic means'] will exempt the following types of experiments:

"An *E. coli* strain is constructed in which a chromosomal gene of *E. coli* has been enzymatically joined to plasmid DNA; this plasmid is then transferred by conjugation into another bacterial host that is not on the Director's List of bacteria that exchange with *E. Coli.*

"It seems logical that this experiment should be exempt, because it involves natural genetic exchange between two organisms both of which are exempt. The *E. Coli.* donor is exempt because it represents a gene combination that could easily arise by natural means. As the transfer can also occur naturally, the same statement applies also to the second host carrying the plasmid.

"If unidirectional plasmid transfer had been accepted as an adequate criterion for inclusion on the Director's List, the strain would be automatically exempt. The reason for not accepting this criterion was that some doubts had been expressed as to whether unidirectional plasmid transfer automatically implied bidirectional transfer of chromosomal genes. However, in the present case, the ability to construct the desired recombinant is *de facto* evidence that it could arise by natural means.

"A specific proposal was submitted to RAC * * * to splice an *E. Coli.* suppressor into an *E. Coli.* transposon, then move the resulting combination into Myxococcus by P1 transduction. This strategy will allow the isolation of suppressible mutants of myxococcus and its phages, which will greatly expedite genetic studies of development and motility in that organism."

The change as proposed by the commentator is warranted in my view, and has been made, with minor rewording for clarity.

There were many comments concerning the list of exchangers in Appendix A to be exempt from the Guidelines under exemption I-E-4.

Many commentators urged more explicit standards for inclusion on the list. As discussed in detail in the section of this document dealing with Appendix A, the criteria for inclusion on the list have been tightened and made more explicit, reducing the list considerably and thus exempting fewer experiments from the Guidelines.

II. Containment

The object of the containment provisions of the proposed revised Guidelines is to ensure that experimental DNA recombination will have no ill effects on the researchers, the general public, or the environment. Public comments on part II of the Guidelines and on the Laboratory Safety Monograph were generally supportive. However, a number of pertinent issues relating to physical and biological containment were raised in correspondence and at the public hearing held on September 15, 1978. They deserve consideration and are addressed below.

PHYSICAL CONTAINMENT

Effectiveness of Physical Containment

One commentator observed that laboratories cannot provide foolproof containment of dangerous organisms and that a biohazard outbreak can rapidly spread to virtually any neighborhood on earth. He cited the recent laboratory accident in England attributed to the escape of a smallpox virus through a faulty filter. NIH agrees that when known hazardous agents are dealt with, the risk of a laboratory-acquired infection cannot be totally eliminated. I believe, however, that adherence to the Guidelines provides ample protection for laboratory personnel, the public, and the environment. Even if an organism should escape from the laboratory, the mutational changes underlying "biological containment" would greatly decrease the probability that it would survive in the environment. The recent incident in England involves an extraordinarily hardy, resistant, and virulent organism to which man is very susceptible—one that is hardly comparable to weakened strains of *E. coli* generally used in recombinant DNA research or to the new host-vector (HV) systems now under consideration.

Laboratory Practices

A correspondent noted that persons on antibiotics or immunosuppressive drugs, or those with open lacerations or chronic digestive abnormalities, are not prohibited from entering the laboratory under any of the physical containment levels. In response, it should be pointed out that the *Laboratory Safety Monograph* (LSM), page 204, provides that "laboratory workers who are undergoing treatment with steroids, immunosuppressive drugs or antibiotics, or are suffering from colitis, ileitis, active chronic diarrhea, or other gastrointestinal disorders, should have a medical evaluation to determine whether they should be engaged in research with potentially hazardous organisms during the time of their illness." Reference to this now appears in Section IV-D-1-h, which also mandates that the institution shall provide health surveillance of laboratory personnel.

Several commentators noted that absence of specific guidance for the rodent and insect control programs required in Section II-B-1-a-(9), II-B-2-a-(12), II-B-3-a-(12), II-B-4-a-(16). The large variety of situations and animal involved makes precise specifications impractical. It is the intent of the Guidelines, however, that adequate attention be paid to this problem, and further guidance will be provided in the next edition of the LSM.

Emergency Procedures

One commentator urged that the Guidelines include specifications for cleanup procedures to be followed in the event of a spill or accidental release of organisms into the environment. A witness recommends that for prompt and adequate response to emergencies, a team of experts from NIH and CDC be formed, and that their names and telephone numbers be published for easy access. Emergency procedures are currently detailed in the LSM, pp. 194-195. These will be expanded in the next edition of the monograph to provide for an NIH-CDC emergency consultation and response program to assist institutions in managing serious accidents. Twenty-four-hour telephone coverage will afford an immediate reponse capability.

One correspondent recommended that all bacteria used in recombinant DNA experiments be tagged so that their spread, in the event of an accident, could be detected in the environment. A general requirement to this effect is not now practicable. It should be noted, however, that in many cases bacteria are tagged to permit identification.

A correspondent raised the prospect that P2 and P3 containment facilities could be compromised by an earthquake. Most institutions have emergency plans for dealing with natural disasters. Selected references are cited in the LSM. If necessary, NIH and CDC are available to provide direct assistance in the management of specific emergency situations. Moreover, institutions in areas subject to natural disasters such as earthquake must generally conform to building code requirements that are designed to minimize the effects of such disasters.

Issues Related to Specific Containment Levels

A number of additional comments were received from public commentators relating to the proposed actions at specific levels of physical containment.

One correspondent said that the new P1 and P2 containment conditions are not significantly different, and that the difference between P1 and P2 should be approximately the same as that between HV1 and HV2. He objected strongly to the escalation of the P1 and P2 containment rules.

NIH believes that the differences between the two levels of containment are significant. For example, P2 requires use of biological safety cabinets to contain aerosol-producing equipment, use of the universal biohazard

sign, and use of gowns, coats, and uniforms. It limits entry into a laboratory to those who have been specifically informed advised of the nature of the research being conducted.

In response to a witness who averred that P1 actually represents *no* containment, it can be noted that P1 is the equivalent of the physical-containment level used in medical microbiological and hospital diagnostic laboratories throughout the world for handling infectious organisms. Indeed, it was suggested that a need exists for an even lower level of physical containment than P1 (for organisms considered of minimal risk). I do not believe it prudent, however, to permit a lower level of containment for experiments covered by the Guidelines.

In the *Decision of the Director* published with the NIH-proposed revised Guidelines on July 28, 1978, I indicated that mouth-pipetting would no longer be permitted in P1 containment. Since it is already prohibited in P2 through P4 containment, this would ban the use of mouth-pipetting for any experiment covered by the Guidelines. One commentor feels that mouth-pipetting should not be prohibited under P2 conditions and should definitely be allowed under P1 containment because of its superior efficiency. The banning of mouth-pipetting at the P1 level, however is in accord with the advice of safety experts; the present availability of excellent mechanical devices for pipetting makes the alternative, in my opinion, a practicable one.

A correspondent suggested that use of biohazard signs at the P2 level of containment should be discontinued: "They should be reserved for demonstrated biological hazards. There is a real danger that overuse of these signs in cases where workers know they do not apply will lead to the ignoring of *all* biohazard signs." While I recognize the concern expressed, I feel it prudent to require the universal sign at the P2 level when recombinant DNA materials are being handled.

For the P3 level of containment, one commentator suggested that an autoclave be within the controlled laboratory area, if not the laboratory itself, rather than merely in the same building. Another commentator makes a similar point for the P2 level. This issue was raised in comments on the revision of the Guidelines proposed by the Recombinant DNA Advisory Committee (PRG-RAC, FEDERAL REGISTER, September 27, 1977). As stated in my *Decision* (FEDERAL REGISTER, July 28, 1978), "* * * an absolute requirement that the autoclave must be within the controlled area is not considered appropriate, since contaminated material can be safely transported. Such a requirement would exclude the use of autoclaves in waste-staging areas that have been conveniently sited to support an entire facility."

A commentor questions for entrance of children into P3 facilities. After considering this issue, I have decided to (1) retain the stipulation that persons under 18 years of age shall not enter a P4 facility, (2) raise the age limit for entry to P3 laboratories from 12 to 16 years of age, and (3) eliminate the age stipulation for P2 laboratories.

A recommendation that the use of a separate centrifuge room or cubicle be provided in a P3 facility to contain spills occasioned by rotor failure has not been accepted. All rooms in the P3 facility must be capable of being sealed to facilitate space decontamination. Modern centrifuges do not present the potential hazard associated with earlier models. Rotor design, operation requirements, the design integrity of the centrifuge well, and the availability of sealed centrifuge cups adequately control the aerosol hazard associated with centrifuging.

Other concerns relating to the P3 level of physical containment have been considered:

- Section II-B-3-c-(7), dealing with ventilation, has been completely rewritten to clarify the intent to permit recirculation of HEPA-filtered exhaust air.
- Section II-B-3-c-(5), which requires that laboratory doors be self-closing, has been deleted. As a correspondent observes, the Guidelines should be worded in such a way as to make facility design compatible with Section II-B-3-a-(1) requiring laboratory doors to be closed while experiments are in progress has been retained.
- A recommendation that the Guidelines be revised to require that booties be worn at all times within the P3 laboratories has not been accepted.

For the P4 level of physical containment, one correspondent would have the Guidelines specifically require the use of gloves. In response, it can be noted that most P4 experiments use Class III cabinets, which are fitted with attached arm-length rubber gloves. As shown in Table II of the PRG-NIH, however, one can work in open-faced biological safety cabinets with augmented biological containment. In this case, the requirement for gloves has now been explicitly set forth by addition of text to Table II.

In response to commentors' suggestions and NIH review, other changes have been made in the Guidelines. For example:

- Sections II-B-1-a-(5), II-B-2-a-(5), and II-B-3-a-(5) have been changed to indicate that eating, drinking, smoking, and storage of foods are not permitted in the "laboratory area in which recombinant DNA materials are handled."
- Sections II-B-2-a-(10) and II-B-3-a-(11) have been changed to mandate the posting of the universal biohazard sign on freezers and refrigerators "or other units" used to store organisms containing recombinant DNA molecules. In addition, the requirement for identifying storage units within the P4 facility with the universal biohazard sign has been included in Section II-B4-a-(15).
- Additional language to clarify the use of the terms "sterilized" and "decontaminated" has been added to Sections II-B-1-a-(3), II-B-2-a-(3), II-B-3-a-(3), II-B-3-a-(8), II-B-4-a-(9), and II-B-4-a-(10).
- The requirement that the laboratory be kept neat and clean has been added to P1; it was already present at P2, P3, and P4.
- A new Section II-B-4-(18) has been added concerning vacuum outlets in the P4 facility.

SHIPMENT

New language to clarify the intent of Section II-C relating to shipment has been suggested by the Department of Transportation. This language has been incorporated (with minor modifications) into the Guidelines. The suggestion of one correspondent that certain clones be exempt from these requirements has not been accepted.

BIOLOGICAL CONTAINMENT

Certification of Host-Vector Systems

Most comments on the biological containment provisions of the proposed revised Guidelines related to development, review, and approval of host-vector (HV) systems other than *E. coli* K-12. In particular, commentators from the scientific community continue to urge development of such alternate systems. Thus, one correspondent wrote, "The anticipated potential of recombinant DNA in agriculture will be difficult, if not impossible, to realize with *E. coli* K-12 host-vector systems. Therefore, it is imperative that attention be given to the development and approval of alternate HV1 systems that may be useful in genetic engineering of plants and invertebrates." Another correspondent wrote, "While many of the regulations do not add to the safety of what are basically safe experiments, they do serve to inhibit the development of new and versatile vector systems * * *. The redundant safety testing program is too onerous, time-consuming, and in our opinion, not scientifically justified."

While I agree that research based on other host-vector systems must proceed, I believe that certification of these systems should be approached conservatively. The new systems raise

ecological and biological issues that must be carefully and thoughtfully addressed. As one correspondent cautions, "We must be very careful when, bolstered by our confidence in *E. coli* K-12 systems, we try to extrapolate to *B. subtilis*, yeast, etc." Two Working Groups of the RAC have recently met to consider alternate systems and to develop more precise and objective criteria for certification.* Many problems, however, persist for setting general standards that could be applied to all organisms. I believe that the process of review and approval described in the Guidelines will allow for full and deliberate examination on a case-by-case basis of putative HV systems and of pertinent ecological and biological issues. This process will, of course, comply fully with NEPA.

In response to one correspondent's suggestion, text has been added to Section II-D-2-a further clarifying the roles of the NIH Director and ORDA in the process of certification.

Data Required for Certification

One correspondent suggested an expansion of Section II-D-2-b-(1), relating to data to be submitted for certification of HV1 systems other than *E. coli* K-12. Specifically, he would require a thorough discussion of the physiological properties of the organism, particularly those related to its reproduction and survival and the mechanisms by which it exchanges genetic information—not simply the range of organisms with which it exchanges. I believe these characteristics to be especially crucial in approval of new systems; accordingly, Section II-D-2-b-(1) has been amended to incorporate this suggestion.

EK1 Systems

One correspondent noted that most host components of EK1 systems used in recombinant DNA research have mutations in addition to those acquired during K-12's laboratory evolution that confer special nutritional requirements, cause recombinants to be defective, or otherwise diminish survival or reduce the likelihood for transmission of recombinant DNA. It has been suggested that use of such mutations should be encouraged. In my view, much of the value of the EK1 host is its flexibility, and it does not seem necessary to explicitly recommend certain strains of *E. coli* K-12 as EK1 strains. The investigator will generally choose the more readily transformable *E. coli* K-12 strains, and many of the characteristics that enhance transformability decrease survival. In addition, by suggesting the use of certain mutations, we may shut off research on others which might prove even more useful and safe.

FLEXIBILITY IN CHOOSING PHYSICAL AND BIOLOGICAL CONTAINMENT LEVELS

One witness and one correspondent questioned the rationale for allowing alternate levels of physical and biological containment. The concept of "flexibility" is discussed at some length in the *Decision* document, FEDERAL REGISTER, July 28, 1978, pp. 33052-33053, and in the accompanying *Environmental Impact Assessment*, p. 33113. Moreover, the flexibility allowed in alternate P and HV levels is carefully explained in the text of the Guidelines, and the investigator must follow the explicit requirements set forth in part III of the Guidelines and Tables I and II.

III. CONTAINMENT GUIDELINES FOR COVERED EXPERIMENTS

GENERAL CONSIDERATIONS

Many of the commentators supported the levels of containment recommended for covered experiments. They concurred with the scientific arguments presented in the Decision document and Environment Impact Assessment (issued July 28, 1978) as a rationale for lowering containment levels. Some cited the reports of the Falmouth and Ascot risk-assessment meetings as confirmatory evidence, and reiterated that *E. coli* K-12 cannot be converted into an epidemic pathogen even by the introduction of additional genes from known pathogenic strains.

Many commented favorably on specific sections of the Guidelines, such as the lowered containment levels for viral DNA. Others supported the proposed containment levels for the cloning of primate DNA. One further stated that relaxation would permit major studies to be made in locating and mapping human genes. Another noted that the proposed revisions would permit the conduct of research with plants and plant-associated microorganisms and endorsed the changes based on the Workshop on Risk Assessment of Agricultural Pathogens.

A number of commentators, while generally supportive of the changes proposed, believed the Guidelines to be still too restrictive. Some urged that they either be dispensed with entirely or, in the opinion of one commentator, be replaced with the following sentence: "It would seem prudent to conduct work with organisms containing recombinant DNA under laboratory conditions appropriate to the degree of pathogenicity of the donor organisms."

I appreciate the thoughtfulness and care that have gone into the many letters. I also acknowledge a belief that the proposed revised Guidelines represent a conservative lowering of containment based on data and analysis discussed in detail in the Decision document and Environmental Impact Assessment of July 28, 1978.

On the other hand, there were commentators and witnesses who believed the lowering of containment levels in the proposed revised Guidelines was not justified. While there was a difference of emphasis in many of the comments, there appeared to be several major concerns. I shall consider each of these in turn.

● Commentators state that "much of the evidence [that NIH cites as a basis for lowering containmant] has never been published or is available only in summary form." Also that "A great deal of weight has been placed on semi-authorized reports of discussions held at closed scientific meetings, attended by a small number of selected participants." They express concern that such action by NIH has prevented the wider scientific community from critical appraisal of the data. Various of these commentators state that the results of the Falmouth conference were published only two months before the proposed revision of the Guidelines was issued, that the proceedings of the Ascot conference have not been issued, and that the results of the Rowe-Martin risk-assessment experiments have not yet been published.

The extensive proceedings of the Falmouth meeting, held in June 1977, were published in the *Journal of Infectious Diseases* in May 1978. Publication in journal form usually involves a considerable delay, even after the edited manuscript, in this case constructed of transcripts of papers and discussions edited by participants, has been completed. The moderator of the Falmouth meeting, Dr. Sherwood Gorbach, Professor of Medicine and Microbiology, Tufts University School of Medicine, summarized the outcome of the meeting in a letter to me on July 17, 1977. (This letter was published as Appendix M to the October 1977 Environmental Impact Statement, and was also published along with letters from other participants in the *Recombinant DNA Technical Bulletin*, Volume 1, No. 1, Fall 1977.)

The report of the Ascot meeting was published as Appendix E to the Environmental Impact Assessment (EIA) in the FEDERAL REGISTER on July 28, 1978, pp. 33159-33167, and previously in the FEDERAL REGISTER on March 31, 1978, pp. 13748-13755: Its introduction says, "A draft of this report was sent to the members for comment and revi-

*The Working Group on Prokaryotic Host-Vectors Other Than *E. Coli* met on September 12, 1978; and the Working Group on Lower Eukaryote Host-Vector Systems met on September 16, 1978.

sion, and this final version is based on the replies of all the participants."

The report of the Virus Working Group, which considered the Ascot Report, was published as Appendix F to the EIA in the FEDERAL REGISTER July 28, 1978, pp. 33167-33174.

The 36 participants at the Falmouth meeting are listed in the report of the meeting (*Journal of Infectious Diseases*, Vol. 137, pp. 613-614, May 1978). Most of the participants were invited by the organizing (steering) committee for the meeting, and the members of that committee are listed on these pages. In addition to invited participants, others arrived uninvited and participated.

The participants and the reasons for holding the Ascot meeting are discussed in my Decision document (FEDERAL REGISTER, July 28, 1978, p. 33060) and in the EIA, p. 33159.

The participants in the Virus Working Group, which met on April 6-7, 1978, to review the report of the U.S.-EMBO Workshop, are described in the EIA. (FEDERAL REGISTER, July 28, 1978, p. 33167). This meeting was announced in advance in the FEDERAL REGISTER on March 17, 1978; it was entirely open and was attended by others than the participants.

The results of the Falmouth, Ascot, and Virus Working Group meetings were discussed at a number of meetings of the Recombinant DNA Advisory Committee (RAC), where they led to recommendations for changes in the Guidelines. All meetings of the RAC have been announced in advance in the FEDERAL REGISTER, have been open to the public, and have been attended by many nonmembers.

The NIH is sensitive to the need for all concerned to have access to the advisory deliberations contributing materially to the substance and use of these Guidelines. Ordinarily, such meetings will be open to the public and announced in advance in the FEDERAL REGISTER. We have become aware that publication in the FEDERAL REGISTER is not sufficient notice for many, and the *Recombinant DNA Technical Bulletin* and other media will be used whenever possible to supplement announcements of meetings and disseminate reports emanating from them. NIH will also continue its publication of all commentary, transcripts of hearings, and other materials relevant to the "public record" of deliberations on the subject of the Guidelines.

Commentators state that the absence of untoward events in five years of experiments with recombinant DNA is not a valid ground upon which to justify the lowering of containment levels.

There is some merit in this objection, but experience to date should contribute to the basis for revision of the Guidelines. When organisms containing recombinant DNA began to be constructed in 1973, it seemed unlikely to most that hazardous organisms would be produced, yet no one knew for sure. No basis for certainty has yet arrived, but some of the fears have justifiably diminished. The results to date have revealed no major biological factor overlooked in the initial analysis that suggests the guidelines should be stricter than they are. Indeed, several separate lines of evidence indicate the probability of hazards to be even lower than originally thought. That no one has become ill is the least impressive of these. More important lines include the following:

1. Numerous analyses and newer data indicating the very low probability that *E. coli* K-12 will establish itself in the human intestinal tract, thus limiting escape of the organisms in numbers sufficient to infect other living things.

2. The now widely made observation that organisms containing recombinant DNA compete very poorly for survival as compared with organisms not containing recombinant DNA. This was an anticipated finding (see October 1977 Environmental Impact Statement) but has now been documented in various instances. It is true even under laboratory conditions designed to be optimal. Only when the growth medium for the *E. coli* cells containing recombinant DNA is specifically designed to impose selective pressure on the recombinant organisms do they outgrow "Natural" competitors. (Selective pressure could be imposed, for example, by the presence of an antibiotic to which the recombinant organisms are resistant but the natural competitors are sensitive.)

3. The repeated observation that genes of higher organisms, introduced into *E. coli* by shotgun experiments, are not generally expressed. Many of the concerns about possible hazards center on the ability of a host cell to synthesize a foreign protein that might be detrimental to an organism with which the host cell comes into contact.

One correspondent said that assigning a higher degree of containment to organisms that are phylogenetically closer to man is unjustified, with the possible exception of clones capable of harboring viral sequences. The correspondent noted that "even if the cloned DNA were highly homologous to human DNA, how is it envisioned that when carried in a bacterial host it would somehow be more dangerous to man than a non-homologous DNA?" The commentator went on to state that the "production of pharmacologically active agents will clearly not depend upon evolutionary similarity to man" and that in fact such products will likely be specified by lower organisms.

In responding, I must note that a primary concern in the original assignment of containment levels was the possibility that viruses capable of propagating in human tissues could contaminate the DNA. The concern is greatest when the DNA donors are primates or other mammals, and so, for these, higher containment levels are provided.

A secondary consideration involves the possibility that the recombinant DNA may itself transform the host. The likelihood of such DNA integrating into the human genome, and consequently undergoing replication and expression, is directly related to the extent of homology between the foreign and host DNAs.

Another reason for making distinctions on the basis of phylogenetic relatedness is that the more closely related the species, the more likely that polypeptide hormones or related proteins would be pharmacologically active.

A more extensive discussion of the issue of phylogenetic relatedness is given in the Environmental Impact Assessment (FEDERAL REGISTER, July 28, 1978, pp. 33102-33104). This matter lies in a crucial area of risk analysis and will undoubtedly continue to be subject of both further debate and improved understanding in the coming months.

Commentators discuss a number of scientific "fears where there remains reason for caution," including that the virulence of *E. coli* may be increased by recombinant DNA, that recombinant plasmids might be transferred to more virulent strains of bacteria, and that bacteria or viruses containing recombinant DNA could cause autoimmune disease.

In reply, I note that these issues are discussed extensively in the proceedings of the Falmouth Conference (*Journal of Infectious Diseases*, May 1978) and in the EIA of July 28, 1978 (FEDERAL REGISTER).

At the Falmouth conference, evidence was presented on the attempts to make *E. coli* K-12 pathogenic. Even the introduction of *Shigella* genes into *E. coli* by nonrecombinant DNA techniques failed to produce a pathogenic organism having any phenotype suggestive of *Shigella*. There was concensus of all participants at Falmouth that *E. coli* K-12, could not be converted into an epidemic pathogen by recombinant DNA techniques.

There are great safety differences between *E. coli* K-12, an attenuated laboratory strain, and wild-type *E. coli*, as discussed in the EIA.

For an EK2 host to be certified as such, "no more than 1 in 10^8 host cells should be able to perpetuate a cloned

DNA fragment under the specified nonpermissive laboratory conditions designed to represent the natural environment, either by survival of the original host or as a consequence of the transmission of the cloned DNA fragments."

A concern expressed by the commentators is that plasmids containing recombinant DNA might be transferred to other, wild-type organisms in the gut. Some appropriate risk-assessment studies concerning this possibility are being carried out. However, the Falmouth report and tests of EK2 host-vector systems present the following data to indicate that the probability of such transfer of the plasmids is extremely low:

1. H.W. Smith, looking specifically for transfer of a conjugative plasmid from *E. coli* K-12 to normal gut flora, could find no evidence that transfer occurred (Falmouth report, pages 655-660). For biological containment to be breached, transfer of a conjugative plasmid to *E. coli* K-12 would have to occur to be followed by transfer of the poorly mobilizable recombinant plasmid from *E. coli* K-12 to other organisms. (Conjugative plasmids themselves are not allowed to be used as vectors.)

2. Gene transfer *in vivo* greatly increases with colonization by both donor and recipient organisms, and colonization by *E. coli* K-12 in general and x1776 in particular is very rare.

3. Mobilization of the plasmids used in recombinant DNA experiments is extremely low, even under optimal *in vitro* conditions.

4. Transfer of the recombinant-containing vector would require a triparental mating *in vivo*, which even under the most favorable of *in vitro* conditions is not a high-frequency event. Such transfer has not been observed *in vivo*.

5. One commentator suggests that transduction might be an important mode of gene transfer. "Generalized transduction" by phage lambda does not occur. Generalized transduction by phage P1 is a low-frequency event (less that $1/10^6$ infected organisms are transduced for a particular marker) under the very best of *in vitro* conditions.

Additional information on plasmid transfer may be found in the Environmental Impact Assessment (FEDERAL REGISTER, July 28, 1978, p. 33123) and the previous October 1977 Environmental Impact Statement, both of which consider the possibility of transfer of foreign DNA from *E. coli* K-12 as well as the ability of *E. coli* K-12 to survive and spread in nature. As noted in both these documents, the maximum probability for transmission of nonconjugative plasmid vectors from *E. coli* K-12 was estimated at "less that 1 to 1016 K-12s surviving per day in the intestine of warm-blooded animals. The probability is even lower in sewers, sewage treatment plants, and waterways." The EIA further states that *E. coli* K-12 survives poorly and is outcompeted by wild-type enteric bacteria.

The concern expressed by the commentators about the possibility of autoimmune disease will only prove true if a series of events occurs. The very low probability of the establishment of *E. coli* K-12 containing recombinant DNA in the intestinal flora is discussed above. In addition, the inserted eukaryotic gene must be transcribed, translated, and transported to a place where it can induce an immune response. These steps are highly unlikely to occur.

RISK ASSESSMENT

NIH is supporting a number of risk-assessment activities. The Rowe-Martin polyoma experiments are discussed elsewhere in this document. In addition, intramural NIH scientists are collaborating with scientists from other institutions testing the virulence in mice of *E. coli* K-12 containing "shotgun clones" of recombinant DNA derived from other species.

A number of contractors of the National Institute of Allergy and Infectious Diseases are testing the biological containment capabilities of various derivatives of *E. coli* K-12. Some are testing the survival and capacity of plasmid and phage vectors to be transmitted to secondary bacterial hosts in the gastrointestinal tract of mice and man. Others are assessing these parameters in model sewage treatment systems and in situations simulating accidential spills and other types of accidental release of the organisms from experimental procedures.

In addition, investigators proposing systems to be certified by NIH as HV1 or HV2 must perform certain specified tests on these systems relevant to their survival and transmission properties. It is also anticipated in the event that investigators request exceptions to the prohibitions for specified clones, NIH will request substantial risk assessment experiments to be performed to evaluate claims of safety.

SPECIFIC CONCERNS

In addition to their general remarks about the experimental section of the Guidelines, many commentators raised questions about the containment levels set for specific experiments. Others suggested clarifying language for certain sections. I have taken all of these recommendations under consideration. In some instances I have concurred and the Guidelines reflect the change. In others I have decided not to act or have deferred actions pending futher analysis and discussion by the Recombinant Advisory Committee. In all cases I have attempted to respond and to explain the decision.

Section III-A-1: Shotgun Experiments

Comments from respondents on this section of the Guidelines reflected diametrically opposed points of view. Some commentators questioned the rationale for lowering of containment levels for shotgun experiments.

Other correspondents took a different view and requested that NIH further reduce the containment level for shotgun experiments. One advanced the argument that "these pieces of DNA in *E. coli* cannot be more dangerous than their original source."

I have decided to retain those levels of physical and biological containment described in the proposed revised Guidelines. I believe the specified containment levels represent a prudent, albeit most conservative, response to the hypothetical hazards. Rationale for them is presented in the July 28, 1978, Decision document and Environmental Impact Assessment.

Risk analysis by NIH is continuing. One important area of analysis involves the appropriateness of higher containment levels for shotgun experiments, with the tremendous dilution of potentially harmful genes, in contrast to purified clones that have been "engineered" for efficient transcription and translation of DNA inserts.

Section III-A-1-a. Eukaryotic DNA Recombinants Including Primates, Other Mammals, and Birds

Twelve commentators, the largest number of comment on a single issue, wrote to express their views on the limitation of P2+EK2 under the proposed revised Guidelines for the cloing in *E. coli* K-12 of shotgun DNA from primates, other mammals, and birds. All requested that the option of P2+EK2 *or P3+EK1* be offered.

One group argues that to restrict cloning of these classes of DNA to P2 + EK2 is inconsistent, since many viral genomes could be cloned at either P2 + EK2 or P3 + EK1. Other respondents pointed out that use of P3 + EK1 conditions would provide adequate containment and would permit the inclusion of lysogenic lambda systems, which cannot be employed in an EK2 system. One stated that propagating DNA fragments in EK1 host-vector systems permits a 5-10 times greater yield of DNA than in an EK2 system. "Thus the advantage of EK2 containment should be weighed against the necessity of handling much larger volumes of cells."

I referred this matter to the RAC at their October 30-31, 1978, meeting. The RAC advised that the phrase "or P3 + EK1" be added to Section III-A-1-a-(3) (i.e., for DNA from birds) and

this has been done. For Sections III-A-1-a-(1) and III-A-1-a-(2) (DNA from mammals), the RAC recommended addition of the phrase "or P3 + EK1 with a non-mobilizable plasmid." Because the term "non-mobilizable plasmid" is not clearly defined, I am not accepting this recommendation at present, pending further review at the next RAC meeting.

Section III-A-2-a. DNA From Virsus of Eukaryotes Into E. Coli K-12

There was considerable comment about various aspects of Section III-A-2-a, extending from general concerns about the reduction of containment levels from viral inserts to detailed and specific recommendations for clarification of certain phrases.

Several correspondents objected to the general relaxation of containment levels for the cloning of viruses. One stated that although the Ascot conference concluded that "cloning of the whole or any part of a viral genome must logically be less dangerous than working with the virus," his view is just the opposite. The arguments presented by this correspondent are (1) whole virus can elicit the production of antibodies, (2) whole virus with its protein coat is subject to a biological barrier which limits infection across species lines, and (3) whole virus is eliminated from the body after infection. In the view of this correspondent, all of these protective devices are subverted by cloning viral genes in a microorganism that may become established in the intestinal tract. He is also concerned that the Guidelines are not sufficiently stringent for cloning subgenomic DNA fragments of viruses. Another respondent indicated that belief that containment experiments involving animal-cell transforming viruses were substantially reduced, based on the supposed inefficiency of infection by naked DNA. She continued by stating that the decision to lower containment did not take into account the results of the Rowe-Martin risk-assessment experiments with polyoma DNA, which showed that naked polyoma DNA when injected into the bloodstream of mice caused a low-level infection.

The recommendations of the Ascot Workshop (Appendix E to the Environmental Impact Assessment), the subsequent Working Group review (Appendix F to the EIA), and the subsequent RAC review took into account the concerns of correspondents about viral containment, but nevertheless recommended lowered containment levels based on the conclusion that cloning of viruses or their fragments in *E. coli* could be no more dangerous than working with the intact virus. The containment levels were set accordingly. The three reasons cited above as to why the cloned virus DNA might be more dangerous than the whole virus apply only to the first infected cell. The DNA would produce disease only if it became virus and spread; thus, the situation becomes the same as the usual virus infection. This possibility was thoroughly considered at Ascot, and is in the summary report of that meeting. Also, the existence of a subgenomic fragment precludes virus production and so effectively prevents the spread of infection.

The Rowe-Martin risk-assessment experiments (still in progress) are designed to compare the infectivity of a recombinant molecule containing polyoma DNA with that of nonrecombinant polyoma DNA and of whole polyoma virus. To date, there are no data available from these experiments which would lead me in any way to revise the judgements of the meetings cited above.

In response to the concern expressed about naked DNA, there is a significant difference in level of infectivity between naked DNA and whole virus particles; naked DNA is much less infectious than the virus. For additional discussion of naked DNA, see part I of this document.

A correspondent stated that there should be some definition as to whether a DNA virus is a transforming or nontransforming virus. To clarify this, a new footnote (37A) has been added to Section III-A-2-a-(1)-(b).

A correspondent pointed out that there are places in Section III-A-2-a where the word "purified" appears without referencing to Footnote 38. This has now been corrected by inserting reference to Footnote 38 where necessary, and inserting the phrase "subgenomic segments that have not been purified to the extent required in Footnote 38" at other places.

A correspondent discussed "EK1CV," defined in Footnote 40 as the "the use of an EK1 host and a vector certified for use in an EK2 system." He points out that certain EK1CV systems provided containment comparable or almost comparable to EK2, while others are only slightly better than EK1. This is true. However, in all cases the level of containment is higher than EK1. The cases in the Guidelines where EK1CV containment is specified as an option were so recommended by the RAC on the basis of the recommendation of the April 6-7, 1978, Virus Working Group (Appendix F to July 28, 1978, Environmental Impact Assessment).

Section III-A-3. Lowering of Containment for Characterized or Purified DNA Preparations and Clones

As in many other sections of the Guidelines, commentators have expressed their opinions in both general and specific terms. A commentators states that there is no information at present to "show any hazard deriving from recombinant DNA or organisms harboring such DNA * * *. In particular, it would seem quite clear that characterized cloned eukaryotic DNA elements in *E. coli* pose no conceivable hazard." Pursuing this line of reasoning, the commentator argues for elimination of regulation and, in particular, suggests that "consideration be given to a change in the Guidelines so that institutional biohazard committees could be empowered to exempt characterization clones from further regulation."

The proposed revisions in the Guidelines empower the IBCs to give approval for a single-step reduction in physical or biological containment upon receipt of evidence of characterized of a clone and its freedom from harmful genes. Further reductions, or cases involving primate DNA or lowering of containment levels below Pl + EK1, require prior approval by NIH. I do not believe it prudent to accept the commentator's recommendation at this time.

Two comments were received on the criteria for the terms "purity" and "free from harmful genes." Once commentator expressed concern over the inadequate definition of these terms. He believes they are not defined with sufficient precision to guarantee uniform decisions, particularly when the authority to lower containment by one step is left with the IBC. The commentator suggests more rigorous criteria for purity (other than 99 percent) and a broader definition of "harmful gene" to include the concept "that genes which might not be harmful when expressed in their original organism could indeed be harmful if expressed out of context in an unrelated organism."

The other correspondent discussed Footnote 41 which requires that the "desired DNA represents at least 99 percent (w/w) of the total DNA in the preparation" before it may be considered "purified." He stated: "Its adoption reflected the supercautious mood prevalent at that time rather than a clear-cut scientific judgement. In my view, requiring that a DNA fragment should be 90-95% pure (as judged by at least two different analytical procedures) to remove it from the shotgun classification is more realistic and no less safe. Requiring that a DNA fragment be >99 % pure prior to cloning asks for the most stringent and detailed documentation without any real advantage."

The term "purity" is very explicitly defined in Footnote 41. The requirement is that the desired DNA must represent at least 99 percent (w/w) of

the total DNA in the preparation. In addition, at least two biochemical or physical procedures are required for verification of purity.

Footnote 3 gives guidance to the IBCs on many factors to be considered before deciding that DNA recombinants are "free of harmful genes." Further specificity seems unwarranted. I believe that to broaden the definition to include the concept of "harmful" when a gene is expressed out of the normal physiological context would be contrary to the intent of Footnote 3. In considering this issue, I have noted that in the proposed revised Guidelines, different terms are used: i.e., in Section III-A-3, "and the absence of harmful genes established"; in Section III-A-3-a, "are free of harmful genes"; in section III-A-3-b, "and there is sufficient evidence that it is free of harmful genes." These have all been changed (also in Footnote 3 and Section I-D-6) to "and the absence of harmful sequences established." I have also decided that the 99 percent criterion should be retained in the present revision of the guidelines; but this point will be reconsidered by the RAC as a possible item for future revision.

Section III-B. Experiments with Other Prokaryotic Host-Vectors

Several correspondents addressed the use of hosts other than *E. coli* K-12. They pointed out that many experiments with such hosts are "inadvertently prohibited," and suggested wording to allow experiments in hosts other than *E. coli* K-12 which do not meet the criteria for HV1.

In the proposed revised Guidelines, experiments with prokaryotic hosts other than *E. coli* K-12 fall into the following classes: (i) Self-cloning, exempted under the exemption I-E-3; (ii) return of DNA segments to non-HV1 host of origin, Section III-B-2; and (iii) use of HV1 systems, Section III-B-1. I agree that there are many safe experiments which fall into none of the above three classes but which should be allowed under specified containment levels. The proposed revised Guidelines, at the beginning of Section III, stated, "* * * (or the assignment of levels to experiments not explicitly considered here) may be expressly approved by the Director, NID, on the recommendation of the Recombinant DNA Advisory Committee (RAC)." This language has been retained in a slightly modified form in the final Guidelines. In addition, similar language is now repeated in a new Section III-B-3 and at the end of Section III-C-5.

A specific example of this type of problem was provided by a commentator who cited experiments he would like to perform involving recombinant DNA from *Bacillus popilliae*, a pathogen for the Japanese beetle, and *Bacillus thuringiensis*, a pathogen of pest caterpillar larvae. He asked for clarification of what containment levels would apply under the proposed revised Guidelines.

The experiment could be considered under several different provisions. If data are submittted on natural exchange of DNA between *B. popilliae* and *B. thuringiensis*, these organisms could be listed in a future version of Appendix A as falling under exemption I-E-4. Or under the new paragraph III-B-3 which has been added to the Guidelines, containment levels could be set for these experiments.

Section III-C. Experiments with Eukaryotic Host-Vectors

A general issue raised by one respondent concerns the stipulation that some experiments will be assigned containment levels on a case-by-case basis. The commentator is concerned that this approach ignores the need for minimumm standards which can serve as a guide for research workers.

I believe that the case-by-case analysis prescribed for many experiments involving the employment of viral DNA as a vector reflects the caution exercised over the use of such DNA. Each such experiment is thus prohibited until the RAC has had a chance to weigh the scientific evidence and propose whether the experiment should proceed and, if so, to assign appropriate physcial and biological containment levels.

I have accepted several other recommendations for changes in this section. Two commentators offered new language for the section dealing with requirements for the employment of defective adenoviruses as cloning vectors. They noted that new mutants of Ad5 or 2 in which the entire transforming region has been deleted have recently been isolated. These mutants can only be propagated in adenovirus-transformed cells. The commentators suggested that the language in Section III-C-1-c-(1)-(a) be generalized to state: "Human adenoviruses 2 and 5, rendered unconditionally defective by deletion of at least two essential genes, with appropriate helper, can be used under P3 conditions to propagate DNA sequences from * * *." I believe this is justified, and the Section has been modified by changing the word "capsid" to "essential."

A correspondent stated that Section III-C erroneously equates nonproductive infections with nonpermissive cells. He pointed out that in certain situations nonproductive infections may result from infection of permissive cells. I agree. Accordingly, the phrase "to transform nonpermissive cells in culture" has been eliminated at a number of places in Section III-C, and more appropriate language has been substituted.

The same correspondent pointed out that in Section III-C the word "intact" is not appropriate because as soon as a foreign sequence is introduced, the viral DNA is no longer intact. I agree. The wording in the relevant sections has been changed from "intact" to "whole."

Section III-C-2, Invertebrate Host-Vector Systems in Which Insect Viruses Are Used to Propagate Other DNA Segments. Section III-C-3, Plant Viral Host-Vector Systems. Section III-C-4, Plant Host-Vector Systems Other than Viruses

I have considered the comments for these three sections in a single group.

A witness questions "the necessity for EPA registration of an entomopathogenic organism in lieu of simply meeting the criteria of EPA for a temporary exemption from a requirement of tolerance in the environment."

In the proposed revised Guidelines published in the FEDERAL REGISTER on September 27, 1977, "baculoviruses which have been registered by the Environmental Protection Agency" are specifically discussed in the section dealing with invertebrate host-vector systems in which insect viruses are used to propagate other DNA segments. The writer is apparently addressing this section and requesting that the EPA registration not be required but merely "the criteria of EPA for a temporary exemption from a requirement of tolerance in the environment." The analogous section (III-C-2) in the proposed revised Guidelines published in the FEDERAL REGISTER on July 28, 1978, does not in fact refer to EPA registration as a specific criterion. It indicates that experiments in which insect viruses are used to propagate other DNA segments will be evaluated on a case-by-case basis by the Recombinant Advisory Committee. Information required for a judgment includes host range restrictions, and infectivity, persistence, and integration of the viral DNA. Data submitted by the requesting investigator on whether EPA has registered a given insect virus or whether it meets the EPA criteria for a temporary exemption from a requirement of tolerance in the environment will be considered by the RAC.

The same witness also questioned the validity of the statement in Section III-C-3 that "the plants should be grown under P1 conditions—that is, in either a limited access greenhouse or plant growth cabinet which is insect-proof" and suggested substitution of the term "insect-restrictive" rather than "insect-proof," since the latter term implies higher containment. I

concur with the recommendation and have made the change.

On the other hand, I do not agree with the opinion of the correspondent who questioned the relevance of P1 or P2 containment conditions to experiments in which recombinant DNA is cloned in higher plants. The correspondent believes that higher plants containing nonviral recombinant DNA should not require any containment. The proposed revised Guidelines (pages 33082 and 33084 in the FEDERAL REGISTER July 28, 1978) specifically define special P1 and P2 conditions for work with plants. I do not believe that recombinant DNA work with higher plants should now be done with no containment at all.

Finally, I have considered the request of two correspondents discussing employment of the tumor insertion plasmid (Ti) of *Agrobacterium tumefaciens* as a cloning vector. They suggest adding the following sentence to Section III-C-4: "Inoculation of hosts with HV1 approved *Agrobacterium* containing the DNA recombinants requires P2 physical containment." I do not believe inclusion of the sentence is warranted at this time. Data on the system can be submitted to the RAC for approval as an HV1 system. If approval is granted, the RAC at that time can recommend the appropriate containment level.

Section III-D. Complementary DNAs

Two correspondents were concerned over the possibility of eukaryotic DNA being expressed in prokaryotic cells. They noted that genes cloned via a shotgun experiment will probably not be expressed because they retain their intervening sequences and the resulting RNA is not likely to be processed. On the other hand, complementary DNA prepared from messenger RNA could serve in turn as a template for synthesis of the same RNA within the prokaryotic cell. They suggest that a "distinction should be made between eukaryote DNA and cDNA formed from mRNA."

In responding, I must note that containment levels for eukaryotic DNA were developed on the assumption that such DNA, no matter what the source, could be expressed. The proposed Guidelines set the same containment levels for eukaryotic DNA and cDNA formed from functional eukaryotic mRNA. For cloning of viral DNA into *E. coli* K-12, however, there are differences in the containment levels depending on whether one is using the viral DNA itself of cDNA from viral mRNA (see Table III). The probable future uses of cDNA copies of functional mRNAs are discussed in the Introduction and Overview of the Director's Decision (FEDERAL REGISTER, July 28, 1978, pp. 33044 and 33047).

Section III-E. Synthetic DNA

A correspondent argued that the discussion of appropriate containment levels for synthetic DNA that codes for harmless polypeptide products "makes no sense." He asks, "Why is any containment required for a harmless product?" and recommends the following alternative language for this section: "If the synthetic DNA sequence codes for a harmless product or if the synthetic DNA is not expressed *in vivo*, the organisms containing the recombinant DNA are exempt (4) from the Guidelines."

In reply, the term "harmless product" refers to the normal toxicity or pathogenicity of the protein and not necessarily to the remote possibility of its otherwise disrupting the physiological balance of the organism in which it might inadvertently be introduced. I believe that the language of the NIH-proposed revision should remain as published, since the three paragraphs describing containment for synthetic DNA clearly describe three distinct concepts. The provisions of Section III-E are consistent with those of III-A-3 dealing with containment levels for purified or characterized DNA.

IV. ROLES AND RESPONSIBILITIES

RESPONSIBILITIES OF THE INSTITUTION (GENERAL)

Institution

The general responsibilities of the institution are to ensure appropriate review and implementation procedures for all of the institution's recombinant DNA activity that is covered by the Guidelines. Below are a number of general institutional responsibilities that were addressed in correspondence and by witnesses at the DHEW public hearing.

Exercising Institutional Authority. Both groups of commentators stated that the Guidelines should permit the institution to set new requirements beyond those of NIH. In the Guidelines, the institution has this authority, and a provision has been added specifically stating that the institution may establish requirements and procedures for the general implementation of the Guidelines, including additional precautionary steps if deemed appropriate. it should be noted, however, that these Guidelines and the standards they embody are conservative and in no way constitute a minimum set of requirements.

Establishing an Institutional Biosafety Committee. Requirements for membership on the Institutional Biosafety Committee (IBC) drew substantial attention in the letters and at the public hearing. Much of the comment was directed to mandating various representation. Some commentators suggested that a local public health official and a nondoctoral person from a laboratory technical staff serve on the committee. Others recommended mandating community leaders who are "in touch with grass roots attitudes," including "environmentalists." Others suggested that the membership reflect the demographic distribution of the community in which the institution is located. Requirements for membership distribution by age, sex, income level, professional background, and other variables were mentioned. It was suggested that at least two members be custodial or janitorial workers. Others recommended that there be at a minimum one physician trained in infectious diseases, one epidemiologist, and one environmental scientist.

Other commentators and witnesses suggested various ratios of scientists and nonscientists serving on the committee. Some urged that one third of the membership represent "the interest of the community" and another third "scientific disciplines related to risk assessment." It was also suggested that nominating procedures be specified for selecting community representatives.

On the other hand, some commentators believed that the proposed revision was presumptuous in mandating lay representation on this committee, especially when the university may already have several lay committees for oversight.

Others suggested that the minimum membership for an IBC be raised from five to seven. The minimum of five members is recommended to take into account small universities with few projects. In these and many other cases, five is sufficient, and it remains as the minimum. Membership recommendations in the revised Guidelines attempt to balance professional expertise with members who represent the interest of the surrounding community. As pointed out by one correspondent, however, the IBC, in contrast to human-subject committees where broad concepts of social and ethical values are considered, is in large part an expert committee whose essential function is to evaluate research protocols in respect to containment levels, using the explicit instructions of the Guidelines. Rigid quotas are not necessary. Indeed, many small academic institutions would have considerable difficulty meeting specified demographic requirements. The IBC criteria are flexible to permit the institution to select a committee capable of fulfilling its responsibilities.

The DHEW Committee carefully reviewed all the comments and considered at great length membership requirements for the IBCs. On balance, it was decided that the interest of the surrounding coummunity could be

served, as one commentator suggested, by "at least two members." In addition, at least 20 percent of the committee shall not be affiliated with the institution and shall represent the interest of the surrounding community with respect to protection of the public health and the environment. Moreover, nomination procedures need not be specified, but should be left to the discretion of the institution for the selection of these members.

With respect to conflict of interest, some commentators recommended that IBC members be prohibited from any direct involvement in recombinant DNA or closely related research unless the member is a laboratory worker. The conflict-of-interest provisions in the Guidelines respond to these concerns while reflecting the paramount need for relevant scientific competence on the IBCs.

A commentator stated that "peer review does not adequately protect the public," citing instances of noncompliance with the Guidelines at two NIH grantee institutions. It should be noted that the two cases in point involved administrative violations and presented no risk to the public health or the environment.

Some of the commentators from the private sector expressed concern that the financial conflict-of-interest statement required in the Guidelines might be interpreted as denying IBC membership to any member of a company. Others felt that a requirement for public members woud present problems of protecting confidential information. However, at a meeting of the DHEW Committee and representatives from the Pharmaceutical Manufacturers Association, it was agreed that public members could and do serve on the committees. Some are asked to sign agreements to honor confidentiality of proprietary and patent information.

Health Surveillance. This area was one of deep concern to some witnesses and correspondents. Witnesses at the September 15 hearing made several suggestions concerning medical surveillance, and correspondents suggested that the term "medical surveillance" be changed to "health-risk surveillance" or "health surveillance." That suggestion has been adopted in the Guidelines.

Several commentators and witnesses urged that health surveillance programs be required in the Guidelines. Concern was expressed that without such a requirement different standards and different programs would result. In addition, there were many suggestions from commentators, including the Occupational Safety and Health Administration (OSHA), about what should constitute a health surveillance program—for example, complete medical histories, periodic medical checkups, and serial serum samples. It was recommended that laboratories be required to keep official OSHA health and safety log forms, and that records be kept of all agents use, all modified organisms created, and all laboratory-acquired illnesses.

Several commentators also called for a clearinghouse, to be established at the Federal level, at which copies of all health surveillance plans and records would be filed. It was urged that NIH maintain such data, including records of workers in laboratories using recombinant DNA techniques, with particular regard to instances of possible work-related illness. There were also several suggestions for a national epidemiologic monitoring and surveillance program to be supported by DHEW. Such programs might, as one commentator suggested, promote national standards for health surveillance specific for each class of organisms and group of experiments. And finally, there were suggestions for ongoing epidemiologic and biostatistical analysis of data as they are accumulated to permit early detection of trends.

I reviewed these issues in the Decision document accompanying the proposed revised Guidelines as published in the FEDERAL REGISTER July 28, 1978. As I noted in that document, the issue of medical monitoring is one of considerable interest to NIH and is not unique to recombinant DNA research. The "state-of-the-art," however, is primitive in terms of effective monitoring of workers' health generally, and particularly in recombinant DNA research, where there is no known hazard.

One commentator noted that the Cambridge, Massachusetts, city ordinance for recombinant DNA research requires the institution, as part of its health surveillance responsibility, to monitor survival and escape of recombinant DNA organisms in each laboratory worker engaged in this type of research, as by the testing of intestinal flora. Intestinal flora sampling is being undertaken at MIT. NIH will follow the MIT program closely. This in not the time, however, to propose extension of that experiment to general practice.

We recognize the need to aid the institutions as much as possible in this important area. The laboratory Safety Monograph provides extensive detail and guidance. It suggests monitoring illnesses, collecting serum samples, and keeping a register of agents handled. Moreover, the Guidelines now require the institution (rather than the principal investigator) to determine, in connection with each project, the necessity for health surveillance of relevant personnel and to conduct a health surveillance program appropriate to the project. And the Memorandum of Understanding and Agreement will include reference to health-surveillance programs associated with the project.

In response to the calls for a national clearinghouse, it should be pointed out that the NIH Office of Recombinant DNA Activities (ORDA) has been designated in the Guidelines to receive, review, and maintain certain medical and accident information. Through ORDA, NIH will have a collection of essential data which should provide the ability to discern if certain experiments result in unique health problems. It is emphasized, however, that for any health surveillance to be truly effective, it must be conducted at the local level.

RESPONSIBILITIES OF THE INSTITUTION (SPECIAL)

The special responsibilities of the institution include establishing general policies, appointing the Institutional Biosafety Committee (IBC), appointing a Biological Safety Officer (BSO) where required, and reviewing and implementing procedures applicable to the submission of the Memorandum of Understanding and Agreement (MUA). A number of commentators and witnesses addressed these requirements.

One commentator recommended that the signature of an institutional offical not be required on the MUA (in Appendix C of the July 28 revision), but that the IBC chairperson should represent the institution. The signature of an institutional official on the MUA is requisite, for that individual is authorized to act for the institution and assume on its behalf the obligations imposed by the Guidelines. If the institution so wishes, however, it may designate the IBC chairperson as the responsible official for MUAs that do not require prior NIH approval. This is newly noted in the Guidelines and the Administrative Practices Supplement (APS), which now incorporates Appendix C.

The correspondent also recommended that MUAs for fellowships, as found in Appendix C, be deleted as an unnecessary duplication of effort. This recommendation is sound, for it is duplicative to require an MUA when the projects are registered. Thus, MUAs will not be required with fellowship applications.

Another correspondent called for clarification of the difference, if any, between the IBC's procedures for review of NIH-funded and non-NIH-funded projects. The information required for NIH- and non-NIH-funded projects in an institution receiving NIH support for recombinant DNA research is similar. Further information on the requirements has been included in the APS. For purposes of IBC

review and monitoring responsibilities, there should be no distinction between NIH- and non-NIH-funded projects.

Another commentator urged that the Guidelines give greater detail on the types of protocol changes for which a new or revised MUA must be sent to NIH. Information proviously contained in Appendix C has now been added to the Guidelines to clarify this point, and further information is contained in the APS.

Another commentator suggested that the institution be required to notify a local Health Systems Agency upon filing an application for Federal support of recombinant DNA research. This is not applicable to HSA responsibilities under section 1513(e) of the PHS Act and therefore is not mandated.

Another correspondent requested that Appendix C be mandated. The test of Appendix C, now in a supplement to the Guidelines (the APS), has been extensively rewritten, and many of its features have been incorporated in the Guidelines for purposes of clarification. I agree that the provisions now in the Guidelines should be mandatory.

Institutional Compliance. A commentator challenged the right of NIH to require an institution to hold that all principal investigators, irrespective of source of funding, must follow the Guidelines. This requirement, however, is vital to the maintenance of uniform standards and is therefore retained. On the other hand, research supported by another Federal Agency need not be registered with NIH when that agency maintains a registry and provides NIH with essential information.

Another commentator suggested delegating responsibilities for all enforcement of the Guidelines to the institution (IBC), with ORDA receiving periodic reports from the committees on the research they are regulating. There are several reasons such a course would be unwise at this time. Exercise of any discretion is a new responsibility for the IBC's. Uniformity and expertise must be demonstrated by verification through NIH review. A great deal of standard-setting, necessarily central at present, is yet to be done through case-by-case analysis.

One commentator requested that the NIH notify both the IBC chairperson and the institution when it was reviewed each action of the IBC according to the imformation submitted on the MUA. This, I believe, would strengthen coordination of compliance efforts. The final Guidelines accordingly require the double notification.

It was also suggested that NIH provides a statement that it has certified the institution and finds it to be in compliance. This request is related to requirements in State regulations that go beyond the Guidelines. However, NIH plans to provide official documentation to institutions in States requiring such information. The subject will be further treated in the APS.

Another commentator urged NIH to devise a system to protect those who report possible violations. This issue was reviewed in my Decision accompanying the proposed revised Guidelines (FEDERAL REGISTER, July 28, 1978, p. 33065), where I noted that grievance procedures for workers under the Guidelines were not considered necessary because OSHA rules and regulations already provide such a mechanism. However, witnesses at the September 15 hearing and comments from OSHA state that the Occupational Safety and Health Act does not cover employees of State and local governments unless the State operates under an OSHA-approved State plan covering health and safety practices and grievance procedures. Only 23 States currently have such plans. But other States presumably have similar statutory protection, and it would be presumptuous of NIH to attempt to detail specific grievance procedures in all jurisdictions. The Guidelines require the reporting of violations and allow the reports to be made to NIH by anyone. The institutions, I believe, will accept such reports in a positive light and as an important aid in maintaining compliance with the NIH standards.

Institutional Biosafety Committee (IBC)

The principal functions of the IBC are to review and oversee all recombinant DNA projects with respect to compliance with these Guidelines and to advise the institution and ORDA whether the proposals and the research so comply. A number of issues concerning IBCs were addressed by the commentators and witnesses at the September 15 hearing, including delegation of authority to the IBCs, public representation on the committee, and public access to its proceedings.

Delegation of Authority. Several correspondents and a number of witnesses at the September 15 public hearing took exception to the delegation of authority to the institutions and their IBCs to act on certain experiments without *prior* NIH approval. One witness noted that there has been a 4 to 15 percent error rate by the IBCs. He also noted that NIH review did not entail inordinate delays, citing the usual review at ORDA as taking only 4 to 5 days. He urged that NIH retain the present two-level system of review requiring prior NIH approval for all projects. The data here do not take into account additional referrals of MUSs between ORDA and various NIH Institutes supporting such research. These have introduced delays of may days or weeks in processing. Other commentators recommended quite the opposite—that greater latitude be given the IBCs to assign containment levels for experiments.

The reason for the delegation of authority is extensively discussed in my Decision and the Environmental Impact Assessment accompanying the July 28 publication of the proposed revised Guidelines. As stated in the Decision document, the increased responsibility of the institution is in response to comments calling for a simpler administrative process and more local responsibility. It is also a recognition of the practical requirements for enforcement of standards for use of such highly varied and complex technology in many institutions spread over a vast area. As stated by the House Committee on Interstate and Foreign Commerce in its report of March 28, 1978, on the Recombinant DNA Act: "* * * the appropriate portions of the administrative requirements of section IV of the NIH Guidelines are a reasonable model upon which the Secretary could base administrative regulations. In particular the current practice in the NIH Guidelines of delegating to local biohazard committees most of the responsibility for the inspection of the facilities and the approval of the specific safety requirements appropriate to each project or activity is an effective and relatively inexpensive administrative mechanism." Thus, the delegation of increased responsibility at the local level is not primarily to facilitate an increased volume of research, as suggested by a commentator, but rather to place this function at the most appropriate location for initial enforcement of the Guidelines. It should be noted, however, that MUAs, before going to ORDA, go to the NIH Institute funding the research, and there have been delays of days or weeks at this level, adding substantially to the time required for processing. We will consider means to simplify procedures so the ORDA can respond in a timely fashion to the institutions.

The DHEW Committee carefully considered the issue of prior NIH approval. On the basis of that review, the Guidelines now specify the circumstances in which prior approval is required, with greater detail provided in the APS. In addition to the five categories of experiments requiring prior approval in the NIH proposal, prior approval is now required, on the recommendation of the DHEW Committee, for the first project to be conducted by an institution and the first project in a facility at P3 containment.

It should be emphasized that while the delegation to the IBCs permits initiation of all other research at the local level, the NIH review and approval of all research under the Guidelines will continue as before. All protocols not found to be in conformance must be modified. Given the slowly increasing sophistication of investigators and IBCs alike, plus the provision in the Guidelines of explicit standards for performance of their duties, I am confident that this delegation will in no sense present risks to the health or the environment.

It should also be noted that some commentators still regard proposed administrative procedures as "excessive and disproportionate when measured against the perceived risks." They are especially concerned that the work of the IBCs is taxing the human and financial resources of the institution. That a burden is placed on the local institutions cannot be denied, but the responsibility is better delegated than retained at the Federal level. As we learn more, there will presumably be less and less need for formality and centralized review in the governance of this research. In anticipation of probable decentraliztion with time, creation of the local capability must begin without delay.

Another commentator urged that the Guidelines be extended to all hazardous biological research. As stated in my Decision of July 28, I do not believe we can or should extend the Guidelines to other research at this time. However, the entire area of laboratory safety is of prime concern to NIH and the subject of constant review and attention. NIH activities in this area are described in the Environmental Impact Assessment published with the Guidelines as proposed in July. It should be noted that some IBCs, as one correspondent pointed out, assume the added duty of monitoring work with known pathogens that is not related to recombinant DNA technology.

In view of the delegation, some commentators urged that there be more financial support for the operations of the IBC. It was recommended that NIH require some percentage of the overhead charged on recombinant DNA research proposals to be earmarked for operation of the IBCs.

Concern has been expressed in the past about the cost of the IBC operations. As stated before, NIH already pays for the operations of such committees through reimbursement of so-called indirect costs of research. I do not believe there is need at this time to separate them from other indirect costs of the institutions.

Reduction of Containment Levels. A number of commentators and witnesses questioned the authority of the IBCs to lower containment requirements for certain experiments. On the other hand, many believe the IBCs should be authorized both to reduce and to raise containment levels. It should be understood clearly that the IBCs' authority to lower containment levels is quite limited and governed by strict standards and procedures set forth in the Guidelines. NIH is notified of all such discretionary actions. It will review them and require that any failures to come up to the standards of the Guidelines will be corrected.

Specifically, the IBC can reduce containment levels only for experiments using purified DNA and for characterized clones. Standards and procedures for the former action are stated in Section III-A-3-a of the Guidelines and in Footnote 41; those for the latter action, in Section III-A-3-b and in Footnote 3. Standards for both actions appear also in the IBC section of part IV of the Guidelines and in greater detail in the Administrative Practices Supplement. Further, it should be noted that NIH approval is required for any lowering of containment levels below P1 + EK1, or by more than one step, or for experiments involving primate DNA.

Specific authority is granted to the institution (Section IV-D-1) to establish requirements deemed necessary for the implementation of these Guidelines. The IBC, then, can raise containment levels. The national standards, however, are very conservative, and in my view, to raise them generally or for characterized clones and purified DNA is unwarranted.

Appeals. Several commentators advocated, in light of the authority delegated to the IBCs, procedures for "appealing a decision of the local IBC against a project or against a certification of facility." The Guidelines do not prescribe an appellate mechanism. A full partnership of investigators and their institutions is intended in maintaining compliance with the Guidelines. The investigators and the IBCs must not be cast in adversary roles, and NIH will make every effort to promote their cooperation. We will be available on request to provide technical advice and consultation with principal investigators and institutional committees alike.

Emergency Plans. The IBC has responsibility to review and approve emergency plans. A number of commentators suggested greater detail in the Guidelines on the emergency procedures to be employed, including specification for cleanup procedures to be followed should there be a spill or accidental release of organisms into the environment. Other commentators suggested that the Guidelines set national standards for the handling of emergency spills. Several urged that the biosafety officer at each institution be charged with responsibility for drafting such plans.

The Laboratory Safety Monograph presents guidance on pages 194-196 on procedures to be followed in emergencies. Some of that information is now included in the Guidelines to emphasize its importance. The monograph will be revised further, in response to comments, to provide greater detail and to include emergency numbers at NIH and the Center for Disease Control that can be called on a 24-hour basis. The two agencies will provide consultation and direct assistance if needed. In addition, the Guidelines specify that the institution shall cooperate with the State and local public health departments and report to them any illness or laboratory accident that appears to be a hazard to the public health. And the IBC chairperson is responsible for notifying the institution and NIH, within 30 days, of problems with the Guidelines, violations, or significant research-related accidents or illnesses, unless the chairperson finds that the PI has done so.

Public Access. Several witnesses at the September 15 hearing and many commentators urged greater public access to proceedings of the IBC. The proposed revised Guidelines required that minutes of the IBC meetings be made available to the public upon request. However, there were several suggestions for further requirements. Witnesses urged that the IBC meetings be publicized and open to the public, except for those specifically dealing with proprietary or other confidential information. Suggestions were made to enchance public participation through evening meetings of the committee and the use of lay summaries of research proposals. Procedures were recommended for announcing IBC meetings. Others recommended that all MUAs and reports of inspections be made publicly available.

The DHEW Committee spent a great deal of time reviewing comments about this portion of the Guidelines. In my Decision accompanying the proposed revision of July 28, I noted that possible discussion of proprietary and patentable information often precludes open IBC meetings. I did urge, however, that local committees have open meetings when possible and that they be publicly announced.

In response to the issues raised, and in view of the increased responsibility given to the local institutions, the final Guidelines require, in addition to public representation on the committee, public access to proceedings of the IBC. Institutes are encouraged to open IBC meetings to the public whenever possible, consistent with the protec-

tion or privacy and propritary interests.

In addition, the IBC is to forward to NIH any public comments made on its actions and the committee's response to them. And all IBC documents that NIH must make available to the public, such as the funded research proposals, are also to be made available, upon request, at the local level. These include reports of serious accidents and of problems with and violations of the Guidelines; also all NIH reports to institutions when MUAs (including modifications of ongoing projects) are not in compliance. Likewise, minutes of the IBC meetings and inspection reports will be made available. The intention of the Guidelines in all these changes is to enhance public accountability at the local level.

Biological Safety Officer

There were a number of comments concerning the roles and responsibilities of the Biologial Safety Officer (BSO). Several witnesses at the September 15 hearing recommended that whenever recombinant DNA research is being conducted at an institution, such an officer be appointed and required to serve on the IBC. It was also recommended that the BSO have a full-time position. The Committee considered the role of the BSO at some length.

The Guidelines do specify that all institutions conducting work at the P3 and P4 levels must have a BSO. The officer is required at those levels because the sophisticated equipment and facilities require special abilities. The Laboratory Safety Monograph (p. 191-193) outlines the qualifications and role. But the Guidelines do not mandate such an officer for P1 and P2 work because the potential risk at those levels is minimal and the expertise readily available for laboratory safety. The Committee concurred with this view.

Other commentators recommended that the Guidelines assign to the BSO responsibility for monitoring, keeping records, and health surveillance. The DHEW Committee reviewed the qualifications of BSOs, noting the absence of certification procedures for such a new and ill-defined discipline. Accordingly, it was agreed that certification requirements should not now be stipulated for BSOs and that flexibility should be encouraged to permit a BSO to have responsibilities for such activities as health surveillance. As noted in the LSM, one can call on the environmental health and safety program at the institution to assist in a variety of the duties suggested for the safety officer.

The BSO is responsible for developing emergency plans, and the NIH will provide assistance for program development. But in my view, it is far more sensible at present to begin emergency plans at a local level than to attempt to develop them on a grander scale until any hazards are better understood. Unless the principal investigator has already done so, the BSO is also responsible for providing reports to the IBC and the institution on problems with and violations of the Guidelines and on all significant research-related accidents and illnesses.

Principal Investigator

As stated in the introduction to part IV, safety involving recombinant DNA molecules depends in the first instance on the individuals conducting the research. The Guidelines are designed to help the Principal Investigator determine the safeguards that should be implemented, and it is his or her responsibility to ensure that the purpose of the Guidelines is fulfilled. A number of the comments were devoted to the PI's role in laboratory safety and training.

Training. Many of the correspondents and several of the witnesses at the September 15 hearing recommended training programs for all laboratory personnel, including custodial personnel, the members of the Institutional Biosafety Committee, the Biological Safety Officer, and all relevant institutional officials. One commentator recommended that laboratory workers in P2 or higher facilities take and pass training courses or demonstrate equivalent competency before working directly with organisms containing recombinant DNA. Further, a centralized and uniform certification process for workers at the P3 or P4 level was advocated. It was urged that the Guidelines not be revised until there are uniform procedures for training certification of all biosafety officers and all recombinant DNA laboratories at the P2 or higher levels. Some suggested the Biological Safety Officer should be responsible for the certification process.

A number of commentators advised further that the Guidelines specify components of training for a program available to all potentially exposed workers. It was also recommended that the PI make available copies of approved protocols that describe potential biohazards and precautions, not only to the research personnel but also to the custodial staff. It was further suggested that NIH and OSHA should jointly sponsor technical and educational programs for IBC members and Biological Safety Officers.

I appreciate the concern regarding the quality and uniformity of training. As I stated in my Decision document (July 1978), NIH is responding to this by placing a high priority on the development of training standards and courses. For example, we are supporting, as noted previously, a working panel of the American Society for Microbiology that is considering standards for training in microbiological techniques for recombinant DNA research. When a report is submitted to NIH, it will be shared with institutions, IBCs, PIs, and BSOs. National certification of proficiency in any research technology is fraught with problems, especially in areas in which knowledge is increasing rapidly.

NIH is already sponsoring and developing courses on these standards of training. For example the University of Minnesota School of Public Health has developed and conducted a series of short courses on "Biohazard Containment and Control for Recombinant DNA Molecules" under the sponsorship of the National Cancer Institute's Office of Research Safety. The objective is to instruct laboratory workers on the principles of safety in the research laboratory and, particularly, on their application to the safe handling of recombinant DNA molecules. To date, six courses have been presented. A total of 221 participants from 97 institutions have attended. They have come from 7 government laboratories, 34 private or industrial laboratories, and 56 universities.

The Office of Research Safety, NCI, is also developing a training course for biosafety officers on practices and procedures for the control of biohazards in the research laboratory. The purpose is to equip biosafety officers with the basic knowledge and skills to carry out effectively the responsibilities specified in the NIH Guidelines. Detailed instruction on methods for evaluating, certifying, and monitoring physical-containment safeguards will be offered. Guidance will also be provided on how to organize, plan, develop, and conduct a comprehensive biosafety program.

NIH plans to further the biosafety training efforts of institutions by providing on-site consultation. The program will be designed to assist institutions and their IBCs, biosafety officers, and laboratory workers in effectively carrying out the requirements of the Guidelines. Biosafety professionals will be available to visit institutions and assist them in evaluating and improving their safety programs. These professionals will also be available to help solve specific problems in physical containment. A principal element of the program will be to promote good laboratory practice and to reinforce its importance.

Training of laboratory workers is a continuous process required under the Guidelines. One commentator expressed uncertainty as to who has the responsibility for seeing that personnel are trained in safety practices and

techniques. The DHEW Committee reviewed this matter, and on the basis of the review, the responsibilities have been clarified. The institution is responsible for ensuring appropriate training for IBC chairpersons and members, laboratory staff, and the BSO. The IBC chairperson will brief the IBC members and provide whatever information on training is required for them to fulfill their responsibilities. To the PI is delegated responsibility for training all the laboratory workers involved in the project.

Safety Practices. The PI is responsible for correcting work errors and conditions that may result in the release of recombinant DNA materials. Several commentators suggested that any accidental release of recombinant organisms, regardless of suspected pathogenicity, be reported to the proper health authorities. The Guidelines now require the institution to report to State and local health departments any significant research-related illness or accident that appears to be a hazard to the public health.

Another commentator suggested that the PI be required to halt ongoing research if any problems result in a failure to meet assigned containment requirements. It was suggested that the research be halted for 24 hours while a report is made to the IBC. The IBC would then certify in writing that the necessary repairs have been made. The Guidelines require reporting and correction of such problems by the investigator, but they do not specify a time limit except that reports must be made to NIH within 30 days on any significant problems with the Guidelines, on violations, and on all significant research-related accidents and illnesses. Nor do they require the IBC to document the reparis. While these mandates are not necessary, the institution should consider setting such policies as deemed necessary. The Laboratory Safety Monograph and the Guidelines contain increased information on health surveillance to assist the PI in his responsibilities in this area.

Exemptions and Exceptions. Another commentator suggests that the PI receive IBC approval before petitioning the NIH for exemptions to the Guidelines or exceptions to the prohibitions. In light of the enhanced responsibilities of the local IBCs, it is appropriate for them to review proposals for exceptions fo the prohibitions, Accordingly, the Guidelines now state that proposals to NIH must be submitted with the concurrence of the IBC.

Proposals for exemptions from the Guidelines deal with alterations in standards applied to all engaged in this research. Scientists may send those proposals directly to NIH for the considerations of the RAC with notice to the IBC. Note of exemptions granted will be sent to all IBCs. Experiments that are exceptions to the prohibitions require approval at the national level, after which they must be reviewed and approved by the IBC. An MUA must then be approved by NIH before the experiment may be initiated.

MUAs. Several commenters suggested that the Guidelines be clarified with respect to the types of experiments that may not be started prior to NIH approval. As noted previously, the Administrative Practices Supplement is responsive to the suggestion, and more guidance is given in the section of the Guidelines on "Institutions" (IV-D-1) to clarify the preparation and submission of MUAs for new and modified experiments.

Publication. The Guidelines recommend that published research articles specify the containment procedures used. A commentator advocates that this be required. The issue has been raised before, and it remains our view that NIH neither can nor should control what must be included in scientific publications.

RESPONSIBILITIES OF NIH (GENERAL)

Due Process Considerations

A number of commentators spoke on the issue of public participation, including how best to inform the public and ensure public access to NIH proceedings. A number of commentators and witnesses at the September 15 hearing focused on the provisions calling for "appropriate notice and opportunity for public comment." Several suggested that those provisions be described in greater detail in the Guidelines. Other commentators urged that labor and environmental representatives, consumer advocacy groups, public health officials, and government agencies with potential regulatory responsibility have full access to decision-making.

Some commentators called for clarification of procedures for certifying host-vector systems. Others asked that the standards and procedures for future Guideline revisions be explicitly stated. Another wanted procedures that clearly set forth public notice and comment in advance of RAC decisions. And another believed the proposed Guidelines "exacerbate the problems of self-regulation" and urged that "HEW supervise the administration and enforcement of the Guidelines."

One commentator suggested a procedural mechanism for minor or partial revisions. He advised that RAC recommendations be published in the FEDERAL REGISTER for comment, and that the comments be taken into account by the RAC before it forwards final recommendations to the Director. Thus, NIH in these cases would act in the light of advice reflecting public views.

Another commentator suggested that each time NIH receives an application for an exception to a prohibited experiment, notice be published in the FEDERAL REGISTER, and that after a public comment period, final notice of agency action should also be published there.

NIH Procedures. The NIH Guidelines of 1976 provided little or no discretion in their administration or revision. As a result, many recommendations by the RAC could not be accepted because of NIH's lack of authority under those Guidelines to approve them. The revision proposed by the RAC in September 1977 attempted to correct this inflexibility by providing for discretion under specified conditions, with procedures set forth to ensure opportunity for public notice and comment. However, the standards and procedures for exercise of discretionary authority in the proposed revision, as many of the commentators pointed out, needed greater definition and clarity.

The commentators' procedural recommendations provided a focus for the DHEW Committee in its intensive review of these issues in the proposed revisions. Other comments from the scientific community, from many witnesses at the public hearing, and from a DHEW meeting with environmental interest groups augmented the efforts to define avenues for appropriate utilization of NIH authorities. On the basis of the comments made in correspondence and at the September 15 hearing, part IV has been substantially revised to provide for public access and participation in NIH activities under the Guidelines. It clearly sets forth the procedures that will govern the exercise of NIH authority.

First, there is a group of major actions for which the NIH Recombinant DNA Advisory Committee (RAC) will advise the Director after an opportunity for public and Federal agency comment. These actions include lowering or assignment of containment levels where the Director judges the action to be major; certification of new host-vector systems; exceptions to the prohibitions; modification of a list of recombinant DNA sources (microorganisms) to be exempt from the Guidelines and other changes in the Guidelines.

For these major actions the following procedures apply. The Director must seek the advice of the RAC and provide an opportunity for public and Federal agency comment. Specifically, the agenda of the RAC meeting citing the major actions will be published in the FEDERAL REGISTER at least 30 days before the meeting, and the Director will simultaneously publish the pro-

posed actions in the FEDERAL REGISTER for comment. In addition, the Director's proposed decision, at his discretion, may be published in the FEDERAL REGISTER for 30 days of comment before final action is taken. The Director's final decision, along with response to the comments, will be published in the FEDERAL REGISTER and the *Recombinant DNA Technical Bulletin.* The RAC and IBC chairpersons will be notified of this decision.

There is a group of lesser actions for which the RAC will advise the Director after a meeting announced as described above. These actions include all interpretations of determinations referred by ORDA, changes and assignment of containment levels, approval of large-scale experiments for rigorously characterized recombinant DNA where the absence of harmful genes has been established, and designation of certain class 2 agents as class 1 for purposes of the Guidelines. The Director's decision will be transmitted to the RAC and IBC chairpersons and published in the *Recombinant DNA Technical Bulletin.*

And finally, there is a group of administrative and scientific functions in the Office of the Director that may be delegated to the Office of Recombinant DNA Activities (ORDA), involving implementation of the Guidelines and their interpretation. Again, decisions by the Director in these matters will be published in the *Recombinant DNA Technical Bulletin,* and notice will be given to the RAC and IBC.

There was considerable Committee discussion on the standards to guide administrative discretion. It was agreed that the Guidelines should set forth a general standard. Accordingly, they now charge the Director to "with each proposed action, through appropriate analysis and consultation, to determine that it complies with the Guidelines and presents no significant risk to health or the environment." For a discussion of NIH efforts in risk assessment, see part III of this document and the Environmental Impact Assessment (Appendix I).

The Guidelines now reflect these roles and relationships in detail and identify all of the responsibilities in cross-reference on the other sections of the Guidelines and to the Administrative Practices Supplement. As indicated above, opportunities are afforded for public access and participation, with formal procedural requirements based on the significance of the discretionary authority. In light of these procedures, hearings by the Director's Advisory Committee may be unnecessary; but if circumstances warrant, the committee can play an oversight role as it has done in the past.

Recombinant Advisory Committee Membership. The correspondents and witnesses at the September 15 hearing who commented on process considerations also expressed opinions on membership of the Recombinant DNA Advisory Committee (RAC). A number of recommendations were made concerning representation. Some witnesses at the September 15 hearing urged that representatives from the regulatory agencies, such as the Environmental Protection Agency, the Food and Drug Administration, and the Occupational Safety and Health Administration, have full voting membership on the RAC. It was also suggested that a representative from the Council on Environmental Quality serve on the committee. The view was expressed that the representation of these agencies on the Federal Interagency Advisory Committee on Recombinant DNA Research could not substitute for their full participation on the RAC. And it was suggested that representatives from the regulatory agencies constitute a subcommittee of the RAC for purposes of considering all future modifications of part IV.

Some Federal agency commentators suggested that representatives from research agencies such as the National Science Foundation, the Department of Agriculture, and the Veterans Administration serve on the RAC, and perhaps be permitted to consider exceptions to the prohibitions in the Guidelines.

Several commentators recommended that representatives from unions and public interest groups serve on the committee. Quotas for membership were also suggested for public interest groups, unions, and nonprofessional laboratory workers. Public interest members might also be permitted to consider exemptions and exceptions to the prohibitions.

There were a number of recommendations concerning professional and scientific expertise. One commentator advocated representation from "knowledgeable specialists in environmental processes and effects on ecosystems and their biota." Other recommended that the committee include scientists from Federal research agencies, scientists critical of the guidelines, and experts in epidemiology, medical microbiology, and clinical infectious disease research. And finally, it was suggested that RAC be advisory to the Department rather than to NIH.

Many of these concerns were raised at the December 1977 meeting of the Director's Advisory Committee (DAC) by witnesses commenting on the revised Guidelines as proposed by the RAC. As I stated in addressing those concerns in my July 28, Decision, I am acutely aware of the need for broad representation on the RAC, and this was considered in the selection of new members.

To ensure fairness, however, nominations for openings on the RAC are publicly and widely solicited. In July 1978 a notice was filed in the FEDERAL REGISTER requesting public recommendations for RAC membership. All nominations are considered in selecting members of the committee. This open nomination process will be repeated annually, and thus NIH will not be the only source of RAC nominations. Further, nominations are being solicited from all agencies represented on the Federal Interagency Advisory Committee.

There was considerable discussion by the DHEW Committee about the membership of the RAC. The present RAC has 16 members, 2 of whom are lay persons. The DHEW Committee agreed that the composition should reflect the requirements set for the IBCs at the local level. Thus, it is required that at least 20 percent of the RAC members shall be persons knowledgeable about such matters as applicable law, standards of professional conduct and practice, public and occupational health, and environmental safety. In addition, it is recommended that one member be a "nondoctoral" person from a laboratory technical staff.

It was also agreed that the scientific representation on the committee should be broadly based to include persons knowledgeable in recombinant DNA technology and biological safety, but also with expertise in the broader disciplines of biology and medicine—i.e., microbiology, molecular biology, botany, ecology, virology, genetics, infectious disease, plant pathology, and epidemiology.

In view of the expanding role and responsibilities of the RAC, it was though appropriate to augment the expertise and representation. Under a new chapter, the RAC will be expanded to 20 members.

In addition, all Federal agencies represented on the Federal Interagency Advisory Committee will have nonvoting members on the RAC. (At present, some research agencies already have liaison members, such as the National Science Foundation and the Department of Agriculture.) These representatives will be nonvoting because of the large number of Federal agencies involved, but they will be participating members encouraged and enabled to present their agencies' concerns on scientific and other issues.

All members of the RAC may participate on the several subcommittees of the full committee. Thus, there is clearly no need to mandate the nature, structure, or function of subcommittees created by the chairperson in consultation with committee members. Finally, the RAC is advisory to the Sec-

retary of HEW and the Assistant Secretary for Health, as well as to the Director, NIH.

Pending the expansion and restructuring of the RAC, no changes will be made in these Guidelines and no decisions will be made requiring the RAC's prior review and advice.

Federal Interagency Advisory Committee and Recombinant DNA Research. A meeting of the Federal Interagency Advisory Committee and Recombinant DNA Research was held on October 12, 1978, to consider agency comments on the proposed revised Guidelines and proposed roles for the committee. Several agency representatives noted that under the discretion granted in the Guidelines, cognizance should be taken of Federal agency roles. Enhancement of the roles for Federal agencies other than NIH was discussed with the committee. This included the proposal of nonvoting membership on the RAC, as noted above, and nominations from the agencies for potential voting members. As defined under the new procedures promulgated in part IV, all Federal agencies through their members will have an opportunity to participate in the RAC proceedings and may file written comments concerning RAC activities. Interagency Advisory Committee members will receive RAC agendas and FEDERAL REGISTER notices.

In additions to participating in the proceedings of the RAC, all agencies represented on the Federal Interagency Advisory Committee are now afforded an opportunity to request a meeting of that committee to consider RAC actions in light of their concerns. Some RAC actions, like a recommendation to release recombinant organisms into the environment, will undoubtedly necessitate a meeting of the Interagency Advisory Committee to provide information and seek concensus. Periodic meetings of this committee will also continue to be held for evaluation of recombinant technologies and their regulation under the Guidelines. (For reference, a list of the agencies represented on the Interagency Advisory Committee is presented in Appendix II.)

Scientifc Counselors for ORDA

ORDA will provide consultation to Federal agencies regarding the Guidelines, and a board of scientific counselors from all Federal agencies that support or conduct recombinant DNA work will advise ORDA on the activities of the Office of the Director, ORDA, and the RAC. A key task for the board will be to ensure a common registry of all federally funded recombinant DNA research.

The DHEW Committee expressed the wish that Federal cooperation continue, and stronly endorsed the new responsibilities of the Federal agencies under the revised Guidelines.

RESPONSIBILITIES OF NIH (SPECIFIC)

Office of the Director

The principal issues here relate to the standards and procedures for governing the discretion of the NIH Director under the Guidelines. All of the responsibilities that the Guidelines assign to the Director are now grouped under "general responsibilities" (for promulgating rules and overseeing implementation of the Guidelines) and "specific responsibilities," which include the opportunity for public and Federal agency comments. This new organization clearly delineates the responsibilities and the procedures and standards to govern the exercise of discretion based on the advice of the RAC and ORDA.

The DHEW Committee discussed the need for periodic review and assessment of NIH's experience in conducting and supporting recombinant DNA research. Accordingly, it was agreed that appropriate language should be inserted in the Guidelines that the Director, at the end of 36 months from their implementation, will report on the Guidelines and NIH experience under them in consultation with the RAC and the Federal Interagency Committee. He will solicit public comment on the draft before transmitting the final report with response to comments to the Assistant Secretary for Health and the Secretary, HEW.

In addition, the Director is now responsible for supporting training programs in laboratory safety for IBC members, Biological Safety Officers, Principal Investigators, and laboratory staff.

Recombinant Advisory Committee

A major concern of the witnesses at the September 15 hearing, and of the commentators on the proposed revised Guidelines, was related to the composition of the RAC, as discussed above. The new procedures clearly guide the discretion of the committee and provide for full public and Federal agency participation. The responsibilities of the RAC have been enhanced, with full access to the public and the Federal agencies. As I stated in my Decision of July 1978 accompanying the proposed Guidelines, the task for all RAC members has been enormous and their work and spirit of cooperation have been exemplary. I look forward to continued cooperation with Dr. Jane Setlow, Chairman, and all of the committee members. Their assistance is vital to the integrity of this research under the Guidelines.

Office of Recombinant DNA Activities

The majority of comments concerning ORDA focused on the office's oversight responsibility. The issues concerning delegation of authority to the IBC's and the role of ORDA in registering not only recombinant DNA activities but other data relating to health surveillance have been discussed in the previous section on local institutions.

There were several comments concerning the need for increased staffing for ORDA to meet the new responsibilities under the Guidelines. Additional staff has been provided, and there will be need for more in light of the new responsibilities of the Recombinant Advisory Committee to solicit public and Federal agencies' comments.

As noted previously in the section on the Interagency Committee, a board of scientific counselors from the other Federal agencies that conduct or support recombinant DNA research will be established as advisory to ORDA. This board is created in response to suggestions from Federal agencies for some mechanism to ensure uniformity in interpretations and determinations made under the Guidelines where discretion is granted. An early task of the board will be to assist in creating and maintaining a registry for all recombinant DNA activities funded by the Federal Government. The board will also assist ORDA's Director in forwarding to the RAC all requests from other Federal research agencies for action on such matters as certification of new host-vector systems. We are, in fact, trying to ensure a capability for uniform interpretation and implementation of the Guidelines throughout the Federal sector.

Another commentator urged that a time-frame be set for implementing the new standards and procedures. This request is a most important one. In anticipation of the release of the Guidelines, procedures have been drawn up for meeting the new requirements. Dr. William Gartland, Director of ORDA, has sent a letter to all institutions, IBC chairmen, and Principal Investigators, specifying the measures to be taken within the next three months to implement the new Guidelines effectively.

Registration. Here the principal comments came from the Federal agencies and private industry. The proposed revised Guidelines require the institutions that receive NIH funds for recombinant DNA research to register all recombinant DNA projects, irrespective of the source of funding. Representatives from Federal research agencies pointed out that institutions should not be required to register with NIH if they are already registering with the Federal agency that supports the work. Accordingly,

the Guidelines now specify that an institution need not register with NIH its projects funded by another Federal agency when that agency maintains a registry and provides the NIH with essential information. The institution will register projects directly with NIH if the supporting Federal agency does not choose to maintain its own registry.

At a meeting held with the DHEW Committee, representatives of the Pharmaceutical Manufacturers Association urged greater protection for proprietary and patent information under the Guidelines. The proposed revised Guidelines offered a system of voluntary registration and certification for the private sector which was not available under the 1976 Guidelines. In addition, a representative from the Commerce Department also urged expansion of the Guidelines to protect proprietary and patent information. On the other hand, environmental interest groups have expressed concern that there be maximum disclosure of information. Because of the complexity of the issue, and the general perception that NIH does not have the powers to completely protect proprietary rights and trade secrets, this aspect of the Guidelines will be handled separately after their issuance. The Food and Drug Administration is now considering issuing regulations that would require drug companies to comply with the NIH Guidelines.

Compliance. Several of the commentators and witnesses at the September 15 hearing recommended stronger language in the Guidelines concerning compliance with the Guideline provisions. The proposed revision stated that noncompliance may result in suspension, limitation, or termination of financial assistance. Several commentators urged that the language be made mandatory. Others suggested that possible violations be ranked, with definite penalties set in each case, including criminal penalties. Still others urged invocation of Section 361 of the PHS Act to ensure compliance through regulation.

Many of these issues were raised at the December hearing of the Director's Advisory Committee and in correspondence on the Guidelines as proposed by the RAC. In response to the suggestions, a section on compliance was included in the proposed revision. However, as I noted in my Decision accompanying that publication, NIH has no authority to impose fines in the absence of new legislation. I also noted that appropriate HEW procedures will be followed should suspension or termination of a grant be necessary. In light of the lack of statutory authority, penalties for negligence and criminal penalties should not be specified. It has been suggested that NIH might seek reimbursement for any funds expended upon activities not conducted in accordance with contractual assurances. This recommendation differs from current HEW grant policy and will require much more consideration.

On the basis of DHEW Committee discussion, a new provision will allow NIH to require prior approval of any and all recombinant DNA research projects if the institution fails to compy with the Guidelines.

Invocation of Section 361 of the Public Health Act has been carefully considered by the Interagency Committee and the Department over the past two years. The most recent expression of interest in this authority was in a letter six Senators requesting Secretary Califano to consider invoking Section 361 to regulate recombinant DNA research. The letter and the Secretary's response are included in Appendix III to this Decision. Briefly, the Secretary said that the Department does not intend to evoke existing statutory authorities to regulate recombinant DNA activities at this time. He went on to quote the Interagency Committee's report of March 15, 1977, dealing with elements for legislation, including the determination that Section 361 would require a reasonable basis for concluding that recombinant DNA research may cause human disease. Such a conclusion is tenuous at best and would at present be an inappropriate basis for invoking the regulation. The Secretary, however, noted in his letter that if the Department had to act speedily, Section 361 is available and would be used. In the Secretary's view, only legislation would justify establishing regulations.

V. Footnotes and References

In reply to correspondents' suggestions and NIH review, minor changes have been made in Footnotes 3 and 5; and five new footnotes—2A, 19A, 33A, 33B, and 37A—have been added.

A correspondent recommended that text be added to Footnote 2 to discuss the basis for allowing cloning of genetic information from *Vesicular stomatitis* virus and moderate-risk oncogenic viruses. Since Footnote 2 already refers the reader to the July 28, 1978, Decision document, where this is discussed in detail, no further discussion in Footnote 2 seems necessary.

Appendix A

(Director's Decision concerning Appendix A of the Guidelines)

There were many comments concerning the list of exchangers in Appendix A to be exempted from the Guidelines under Exemption I-E-4.

Some correspondents recommended additions to the list, including *Caulobacter crescentus, Agrobacterium, Proteus,* and *Xanthomonas.*

On the other hand, some correspondents felt that there was insufficient documentation for the entries on the list and that the list should be by species, not genus.

One correspondent recommended citing Bergey's *Manual of Determinative Bacteriology.* Another wrote, "It is also questionable why one should list *Escherichia coli* exchangers and not others in nature such as the organisms that exchange with *Bacillus subtilis,* with *Haemophilus influenzae,* with *Neisseria gonorrhoeae,* etc."

In response to the many comments received, the list of organisms to be exempt from the Guidelines under Exemption I-E-4 has been carefully reconsidered. The discussion below attempts to make more explicit the considerations used in constructing this list. In addition, the criteria for inclusion on the list have been tightened, reducing the list considerably and thus exempting fewer experiments from the Guidelines. References supporting the entries to the list are given below (refs. 1-22). The final list (Appendix A) closely resembles the "first list" described in Appendix D to the July 28, 1978, Environmental Impact Assessment.

It should be emphasized that the evolution of this list will continue as more experiments are done and as we gain more knowledge in this rapidly advancing field. In addition, other organisms recommended by some of the commentators (*Bacillus* or *Haemophilus* species, for instance) are currently being considered by the RAC for future inclusion under this exemption.

As noted in Appendix D to the July 23, 1978, Environmental Impact Assessment: "The natural transfer of genes between bacteria occurs by transduction (bacterial virus-mediated), transformation (uptake of isolated DNA by a bacterial cell), or conjugation (plasmid-mediated transfer of genes between bacteria requiring cell-to-cell contact). A reasonable generalization is that virtually all closely related species of bacteria can exchange genes by transduction and transformation, the former limited by the relatively narrow host-range of transducing bacteriophage and the latter by the requirement, in the case of chromosomal DNA, for homology of DNA in most recombination events. Conjugal mating with exchange of DNA can occur between virtually all Gram-negative bacteria, including naturally occurring soil and intestinal species, when mediated by a plasmid of broad host-range (for example, the Inc P-1 group plasmids). Recently, conjugal mating has also been shown to occur between strains of certain species of *Streptococcus,* a Gram-positive organism (for example, *Streptococcus faecalis*). To date, however, conjugal mating has not been demonstrated between Gram-negative and Gram-positive bacteria.

"The relatedness of different microbial species can be estimated by determining the extent of DNA homology between them or by studying the properties of different microorganisms in genetic crosses. As a general rule, organisms that show considerable homology of their nucleotide sequences under a standard set of experimental conditions have the capacity to mutually integrate chromosomal genes. For example, in the case of the *Enterobacteriaceae* family of bacteria (includes *Escherichia coli* K-12), there is both extensive DNA-DNA homology (1) and chromosomal gene exchange (2) with a reasonable correlation between the degree of DNA-DNA homology and the capacity to mutually integrate chromosomal genes.

"Genetic relatedness, as indicated by a high level of DNA-DNA homology between different microorganisms, is not, however,

an absolute requirement for the exchange of chromosomal genes between bacteria. In fact chromosomal gene transfer among diverse members of the Gram-negative group of bacteria has been demonstrated where the microorganisms involved show little or no DNA-DNA homology. In these cases the exchange of chromosomal genes is promoted by a broad-host-range plasmid of the Inc P-1 incompatibility type. These plasmids mobilize the chromosomes of a wide variety of Gram-negative bacteria, incorporate segments of these chromosomes, and are capable of establishing themselves along with covalently linked chromosomal genes in a wide range of Gram-negative bacteria. (3)"

In evaluating a pair of organisms for inclusion as nonnovel exchangers, we are making an estimate of the probability that the combination of genes might have occurred naturally. If the combination is not a new one, then there should be no special hazard in creating such an organism by recombinant DNA technology. Thus we can exempt this combination from the Guidelines.

Any conclusion about exchange between organisms involves some extrapolation from the experimental data available. We have tried, in the discussion below, to make explicit these extrapolations and the scientific bases for making them. For this purpose, the types of criteria which might be taken into account in preparing a list of exchangers are divided into four categories. The first two were those used in constructing Appendix A in these final revised guidelines. The first three were used in constructing the version of Appendix A which appeared in the July 28, 1978, proposed revised guidelines. All four were used in constructing a list approved by the RAC and described as the "third list" in Appendix D to the July 28, 1978, Environmental Impact Assessment.

1. *Organisms which exchange chromosomal genetic information which becomes stably integrated into the host chromosome.* This, the most stringent criterion for exchange, requires significant homology between recombining segments. Organisms which meet these criteria will therefore be closely related by DNA homology measurements (Ref. 1, 2). In addition, more than one mechanism of genetic exchange may be found (i.e., transduction and plasmid mobilization), and transfer of many different markers may be demonstrated. The major extrapolation involved in this category is the extension of data from one strain to others in the same species or genus. In the Appendix A list, most of the entries are listed as genera (*Shigella, Salmonella,* etc.), while the *Pseudomonas aeruginosa* species is listed. One can generalize from species to genus when there is evidence that all members of the genus behave similarly, and show extensive DNA homology. In addition, in some cases, exchange has been demonstrated in many species of the genus. The DNA homology test is convincing for *Shigella,* but not for *Pseudomonas.*

2. *Organisms which exchange chromosomal information that is not necessarily integrated into the chromosome of the recipient (for instance, transfer via F' or R).* This sort of exchange can occur in the absence of extensive DNA homology between the organisms, and requires only that the plasmid and its chromosomal genes be maintained in the recipient organism.

Although two organisms meeting these criteria might not be closely related, this type of exchange is probably the best model of a recombinant DNA experiment. In both cases, relatively small amounts of genetic information are transferred, usually in plasmid form, to an otherwise "foreign" genetic background. Therefore, it seems reasonable to accept evidence of such exchange as grounds for exemption.

Criteria 3 and 4 deal specifically with Inc P-1 plasmids, but the principles can be extended to other exchange mechanisms.

3. *Organisms which show evidence of a plausible mechanism for exchange (e.g., R' formation or evidence of mobilization of chromosomal genes by an Inc P-1 plasmid.)* In this case, the plasmid itself has been shown to move from organism to organism. It has been shown to pick up chromosomal genes, but the transfer of these chromosomal genes in interspecies matings has not necessarily been demonstrated.

To endorse these criteria, we must extrapolate from the transfer within the species to more distantly related organisms. For such an extrapolation, one must assume that no barriers will exist for R' transfer that do not exist for transfer of the plasmid itself. In many tested cases, this is clearly true: transfer of chromosomal genes incorporated into an R factor is comparable in frequency to transfer of the plasmid itself, and the R' can be moved to a broad range of organisms (4). However, this may not be universally true (5).

4. *Organisms whch can receive or donate broad host range plasmids.* Since these plasmids are known, in many cases, to mobilize the chromosome and transfer chomosomal genes, such transfer might be expected for any organism that receives or donates the plasmid. This extrapolation assumes that (i) chromosomal pickup is always able to occur with these plasmids and (ii) transfer of chromosomal genes to other species will occur (this latter case is the same at that analyzed under criterion 3).

Analysis of the basis for the first extrapolation would include consideration of the numerous cases where such mobilization and transfer can be detected (see, for instance, ref. 5-10) and those few where it cannot (11).

It is my decision that the data supporting the use of criteria 3 and 4, while suggestive, are not yet compelling enough to warrant exemption from the Guidelines for recombinant DNA experiments. As more data are accumulated, this conclusion will be carefully reconsidered.

The Issue of Two-Way Exchange

The organisms listed in appendix A fit the first two criteria described above—i.e., in all cases, there is direct evidence of chromosomal exchange between two species on the list, and many show extensive DNA homology as well. In addition, for all the organisms on this list, exchange can be demonstrated in two directions. Further, if organisms A and B both exchange genetic information (both donate and receive) with a third organism—*E. coli* K-12, for instance—then *E. coli* K-12 can act as a path for the DNA of organism A to reach B, and *vice versa.* Thus, the requirement for two-way exchange allows us to exempt recombinants made between A and B. Therefore, we have exempted "any recombinant DNA molecules that are (1) composed entirely of DNA segments from one or more of the organisms listed below and (2) to be propagated in any of the organisms listed below."

It would make sense, of course, to have one-way lists as well, where cloning exempt from the Guidelines would only be allowed in the recipient. The creation of such lists will be considered by the RAC.

REFERENCES

1. Brenner, D. J. (1977). *Characterization and Clinical Identification of Enterobacteriaceae by DNA Hybridization.* Progress in Clinical Pathology 7:71-118.

2. Sanderson, K. E. (1976). *Genetic Relatedness in the Family Enterobacteriaceae.* Ann. Rev. Microbiol. *30* :327-349.

3. Holloway, B. W. (1978). *Plasmids Which Mobilize Bacterial Chromosomes.* Plasmid, in press.

4. Dixon, R., F. Cannon, and A. Kondorosi (1976). *Construction of a P Plasmid Carrying Nitrogen Fixation Genes From Klebsiella Pneumoniae.* Nature *260* :268-271.

5. Johnston, A. W. B., S. M. Setchell, and J. E. Beringer (1978). *Interspecific Crosses Between Rhizobium leguminosarun and Rhizohium meliloti: Formation of Haploid Recombinants and of R-Primes.* J. Gen. Microbiol. *104:* 209-218.

6. Beringer, J. E., S.A. Hoggan, & A. W. B. Johnston (1978). *Linkage Mapping in Rhizobium Leguminosarum by Means of R Plasmid-Mediate Recombination.* J. Gen. Microbiol. *104:* 201-207.

7. Sistrom, W. (1977) *Transfer of Chromosomal Genes Mediated by Plasmid R68.45 in Rhodopseudomonas sphaeroides.* J. Bacteriol. 131:526-532.

8. Haas, D., and B.W. Holloway (1978) *Chromosome Mobilization by the R Plasmid R68:45:A Tool in Pseudomonas Genetics.* Mol. Gen. Genetics *158*:229-237.

9. Towner, K.J. (1978). *Chromosome Mapping in Acinetobacter calcoaceticus.* J. Gen. Microbiol. 104: 175-180.

10. Stanisch, V.A., and B.W. Holloway (1971). *Chromosome transfer in Pseudomonas aeruginosa Mediated by R Factors.* Genet. Res. 17:169-172.

11. Alexander, J.L., and J.D. Jollick (1977). *Transfer and expression of Pseudomonas Plasmid RP1 in Caulobacter.* J. Gen. Microbiol. 99:325-331.

12. Baron, L.S., P. Gemski, E.M. Johnson, and J.A. Wohlhieter (1968). *Intergenic Bacterial Matings.* Bacter. Reviews 32:362-369.

13. Cannon, F.C., R.A. Dixon, J.R Postgate, and S.B. Primrose (1974). *Chromosomnal Integration of Klebsiella Nitrogen Fixation Genes in E. coli.* J. Gen. Microbiol. *80*:227-239.

14. Chatterjee, A.K., and M.P. Starr (1973). *Gene Transmission Among Strains of Erwinia Amlovora.* J. Bact. 116:1100-1106.

15. Chatterjee, A.K. and M.P. Starr (1973). *Transmission of Lac by the Sex Factor E in Erwinia Strains from Human Clinical Sources.* Infection and immunity 8:563-572.

16. Denarie, J., C. Rosenberg, B. Bergeron, C. Boucher, M. Michel, and M. Barate de Bertalmio (1977). *Potential of RP4:Mu Plasmids for In Vivo Genetic Engineering of Gram Negative Bacteria.* In Bukhari, A.I., J. A. Shapiro, and S.L. Adhya (editors); *DNA Insertion Elements, Plasmids and Episomes,* Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.

17. Faelen, M., A. Toussaint, M. Van Montague, S. Vander Elsacher, G. Engler, and J. Schell (1977). *In Vivo Genetic Engineering: The Mu-Mediated Transposition of Chromosomal DNA Segments onto Transmissible Plasmids.* In Bukhari, A. I., J. A. Shapiro,

and S.L. Adhya (editors), *DNA Insertion Elements, Plasmids and Episome*, pp. 521-530, Cold Spring Harbor Laboratory, Cold Spring Harbor, N.Y.

18. Goldberg, R. B., R. A. Bender, and S. L. Streicher (1974). *Direct Selection for P1-Sensitive Mutants of Enteric Bacteria.* J. Bact, *118*:810-814.

19. Hedges, R. W., A. E. Jacob, and I. P. Crawford (1977). *Wide Ranging Plasmid Bearing the Pseudomonas Aeruginosa Tryptophan Synthetase Genes.* Nature *267*:283-284.

20. Johnson, E. M., B. P. Placek, N. J. Snellings, and L. S. Baron (1975) *Conservation of Salmonella Typhimurium Deoxyribonucleic Acid By Chromosomal Insertion in a Partially Diploid Escherichia Coli Hybrid.* J. Bact. *123*:1-6.

21. Nagahari, K., Y. Sano, and K. Sakaguchi (1977). *Derepression of E. Coli trp Operon on Interfamilial Transfer.* Nature *266*:745-746.

22. Signer, E. R., a. Torriani, and C. Levinthal (1961). *Gene Expression in Intergeneric Merozygotes.* Cold Spring Harbor Symp., Quant. Biol. *26*:31-34.

APPENDIX B

(Director's Decision concerning Appendix B of the Guidelines)

Three correspondents correctly point out that since the publication in 1974 of the "CDC Classification of Etiologic Agents on the Basis of Hazard" (which is repeated verbatim as Appendix B to the Guidelines), *Actinomycetes* have been reclassified. Formerly considered to be fungal agents, they are now considered bacterial agents. An explanatory footnote has been added to the table.

APPENDIX I—ENVIRONMENTAL IMPACT ASSESSMENT

ENVIRONMENTAL IMPACT OF THE FINAL GUIDELINES

An *Environmental Impact Assessment of the NIH-Proposed Revised Guidelines* (EIA) was published with the Guidelines in the FEDERAL REGISTER of July 28, 1978. The assessment was based on an intensive analysis of the Guidelines then in effect, the Guidelines as proposed by the Recombinant DNA Advisory Committee in September 1977, and the Guidelines as proposed by NIH in July 1978. The conclusion of the assessment was that there would be no adverse impact of the NIH-proposed changes upon the environment.

The issues raised by the commentators in correspondence and by the witnesses of the September 15 hearing on the NIH-proposed revised Guidelines are reviewed in detail in the accompanying Decision document. It is the conclusion, based on that review of the alternatives proposed in July 1978 and the decisions reflected in the final Guidelines, that there will be no adverse impact of the Federal actions upon the environment. Indeed, in the extensive revision of part IV, these final Guidelines enhance public participation and accessibility at the national and local levels, with increased emphasis on health surveillance and safety training. The final Guidelines provide an even stronger framework to ensure that no significant risk is presented to the public health or the environment.

Consideration now follows of certain issues relating to the EIA of July 28, 1978, which were raised in correspondence and by witnesses at the September 15 hearing.

NEPA Considerations

A witness at the September 15 hearing cited the EIA as being inadequate and held that a full Environmental Impact Statement (EIS) should be prepared. The witness stated that an EIS is clearly required by the law. In addition, the witness found the EIA inadequate in its analysis of the revisions in such areas as exemptions and the use of *E. Coli.* K-12 and other host-vector systems.

In our view, the EIA prepared by NIH on the proposed revisions to the NIH Guidelines fully satisfies the requirements of the National Environmental Policy Act of 1969 (NEPA).

The current Guidelines on Recombinant DNA Research were issued on June 23, 1976, and published in the FEDERAL REGISTER on July 7, 1976 (41 F.R. 27902). They were developed by NIH after opportunity for public comment and an open meeting at which members of the public were invited to testify (41 F.R. 2105).

In the Decision of the Director, NIH, which accompanied the 1976 Guidelines, it was indicated that NIH would prepare a draft EIS on the Guidelines in order to give the public further opportunity to comment. The draft EIS was published in the FEDERAL REGISTER on September 9, 1976, with a preamble soliciting public comment (41 F.R. 38426). After the close of the comment period, a final EIS was prepared, taking into account the comments received and scientific developments up to that time. The EIS actually became final on November 28, 1977, when notice of its receipt was published in the FEDERAL REGISTER by the Council on Environmental Quality (42 F.R. 60588).

During this period, scientific evidence has been accumulating that the risks presented by recombinant DNA research, which has always been purely speculative, were indeed remote. As a result, it became apparent that the restrictions in the Guidelines were more stringent than necessary and that the Guidelines needed to be revised. The process of revision was first undertaken by NIH's Recombinant DNA Advisory Committee (RAC), which referred a proposal for revision to the Director, NIH, in September 1977. On September 27, 1977, the Director published the RAC's proposal in the FEDERAL REGISTER for public comment (42 F.R. 49596). At the same time, and in a subsequent FEDERAL REGISTER notice (42 F.R. 59918), the Director announced a two-day meeting to secure public testimony on the RAC proposal. This meeting was held on December 15-16, 1977, and witnesses appeared from environmental groups, the scientific community, and industry.

Based on the comments received and the testimony at the December meeting, the Director developed an NIH-proposed revision of the Guidelines (referred to herein as the PRG), relying in part on the RAC proposal. The PRG was issued by the Director, as a proposal, with the approval of the Secretary, on July 19, 1978, and published in the FEDERAL REGISTER on July 28, 1978 (43 FR 33042), the preamble to the PRG requested public comment, announced that a further hearing on the PRG would be conducted on September 15, 1978, before an HEW panel chaired by the General Counsel, and indicated that final action on the PRG would be taken after the panel had reviewed both the written comments and those provided at the hearing.*

When the PRG was published on July 28, it was accompanied by a detailed EIA, which included a discussion of the risks and benefits of recombinant DNA research and an analysis of the current Guidelines, of alternatives to the Guidelines, and of NIH's PRG. In addition to an overall assessment of the environmental impact of the PRG, sepaate environmental impact analyses were made of each section. The conclusions reached were summarized at the beginning of the EIA as follows:

> As can best be determined from all evidence compiled to date and analyzed in numerous scientific and public forums, there will be no adverse environmental impact from recombinant DNA research conducted under the Director's proposed revisions. The Environmental Impact Statement on NIH Guidelines for Research Involving Recombinant DNA Molecules, issued in October 1977, predicted that the environmental impact of research conducted under the 1976 NIH Guidelines would be the continued protection of the laboratory worker, the general public, and the environment from conjectural hazards. So far, this prediction has been confirmed: We know of no scientists conducting recombinant DNA research in the United States or other countries who are not following the NIH or comparable guidelines, and no untoward effect of the research has been reported. Meanwhile, new scientific evidence as well as extensive experience in operating under the NIH Guidelines indicate that revisions are in order. The predictable effect of continued use of recombinant DNA techniques under the Director's proposed revisions would be a greater realization of the benefits of this valuable tool without compromise of safety. (43 FR 33096).

The EIA prepared by NIH on the PRG discusses in detail scientific developments regarding recombinant DNA research. It justifies the changes proposed by NIH, explains why some RAC and public proposals were not ac-

* More than 30 persons from environmental groups and the scientific community testified at the September 15 hearing.

cepted, and assesses at some length the anticipated environmental effects of the changes NIH proposed to make.

In my view the EIA represents a conscientious, thoughtful, and thorough effort to carry out our responsibilities under NEPA. As one correspondent noted, the assessment is a "thorough and fully documented analysis * * * that describes the technical aspects of this research and its conjectural risks and benefits." The EIA took a "hard look" at the current Guidelines, the various alternatives, and the environmental implications of the proposed changes. By soliciting public comment and conducting a public hearing, relevant areas of environmental concern were identified. I believe that a convincing case is made in the EIA that the proposed changes would have no significant environmental impact.

My Decision accompanying these final Guidelines reviews at some length exemptions from the Guidelines in light of the comments made by correspondents and witnesses. And indeed, a lengthy analysis of the list of exempt organisms in Appendix A documents the prudence and caution in which NIH is proceeding. On the basis of comments, the list has been modified and the scope of experiments restricted.

It was also asserted by witnesses that the filing of an EIS would provide for public input in the Government's decisions affecting the environment. In my view, NIH's overall response to the issues raised by recombinant DNA research has been to ensure a full public hearing of all issues. When these issues first arose, NIH conducted public hearings, solicited public comment, developed Guidelines, and published an EIS, which ultimately received judicial approval.

Since that time scientific evidence has shown that the initial concerns about the hazards of this research may have been exaggerated. Accordingly, we proposed to relax some aspects of the Guidelines. In doing so, we again conducted hearings and solicited public comment. And the NIH-proposed revised Guidelines were published for comment, followed by a hearing under the aegis of a DHEW committee chaired by Peter Libassi, the DHEW General Counsel. In addition, all of the proceedings and all documents have been published in an ongoing series of volumes that document the basis for NIH policies. The documents contain relevant proceedings of the executive, legislative, and judicial branches. A fourth volume will be published in January containing the transcript of the September 15, 1978, hearing, all correspondence received by NIH commenting on the proposed Guidelines of July 28, 1978, and all other relevant documents.

RISK ASSESSMENT

Several witnesses raised issues concerning the concepts of risk and safety as outlined in the Environmental Impact Assessment (EIA). One witness emphasized the concept of risk as "a relatively objective measurement of hazards" and safety as "a subjective expression of the level of risk which is acceptable to a population." He believes the NIH Guidelines and Assessment confuse these two concepts. The Guidelines, in his view, do not provide adequate institutional mechanisms to ensure that the value issues involved in safety are thoroughly aired by the general public. Thus, because safety is "value-laden, subjective, and in a sense, political," the Guidelines must reflect these values by ensuring adequate mechanisms for determining safety standards and their implementation.

The October 1977 EIS on the original NIH Guidelines and the July 1978 EIA on the proposed revisions address in great detail occupational and environmental health and safety concerns. As noted in the EIA (FEDERAL REGISTER, p. 33131, middle column), several changes are proposed in the revised Guidelines "in the implementation, review, and monitoring of recombinant DNA activities at the local and national levels, to insure appropriate safety practices and procedures that would minimize any significant environmental impact."

These modifications focus on a restructuring of roles and responsibilities. The applicability of the Guidelines has been extended to all recombinant DNA reseach at institutions that receive any recombinant DNA research support from NIH. Biosafety committees have been given broader responsibilities. At the request of several commentators, Appendix D to the original Guidelines has been revised and updated as *Laboratory Safety Monograph—A Supplement to the NIH Guidelines.* The monograph is a compendium of useful safety information, including instructions on emergency procedures, laboratory techniques for biohazard control, and decontamination and disposal methods. It provides much detail on the responsibilities of the local institution for safety practices and procedures. The impact of these actions and the restructuring of part IV of the Guidelines will be the promotion of safer conduct of this research, affording a greater measure of protection to the environment, with emphasis on occupational health and safety.

Several commentators also urged NIH to initiate and fund a comprehensive risk-assessment program to provide a scientific basis for defining appropriate containment requirements for recombinant DNA experiments. The DHEW Committee reviewed NIH efforts in this regard. It was noted that recombinant DNA research experiments provide a great deal of information on risks. In addition, NIH is supporting a number of studies in risk assessment. The participants at the Falmouth Conference* recommend studies in six areas, and NIH is following up on those recommendations.

The Rowe-Martin polyoma experiments are discussed in the Decision Document. In addition, intramural NIH scientists are collaborating with scientists from other institutions in testing the virulence in mice of *E. coli* K-12 containing "shotgun clones" of recombinant DNA derived from other species.

A number of contractors of the National Institute of Allergy and Infectious Diseases are testing the biological containment capabilities of various derivatives of *E. coli* K-12. Some are testing the survival and capacity of plasmid and phase vectors to be transmitted to secondary bacteial hosts in the gastrointestinal tract of man and mouse. Others are assessing these parameters in model sewage treatment systems and in situations simulating accidental spills and other types of accidental release of the organisms for experimental procedures.

In addition, invistigators proposing systems to be certified by NIH as HV1 or HV2 must perform certain specified tests on these systems relevant to their survival and transmission properties. It is also anticipated that if investigators seek exceptions to the prohibitions for specified clones, NIH will request substantial risk-assessment experiments to be performed to evaluate claims of safety.

Another commentator noted that Dr. Sidney Brenner of the Medical Research Council's Laboratory for Molecular Biology in Cambridge, England, had stated that he believed the whole method of risk-assessment up to now is "fragmentary" and that what is needed is a "more systematic approach," which he was trying to take. Dr. Brenner, when asked for more information on his studies, explained that the method of risk-assessment he referred to is not a new experimental approach but a new analytical approach. Dr. Brenner's work will be followed closely for any new information that sheds light on potential risks or safety of experiments under the Guidelines.

SOCIAL ETHICS

A witness at the September 15th hearing noted that "the steps taken to insure containment are of great immediate importance and the present guidelines should be continued." But

*See Journal of Infectious Diseases, 137:704-708, May 1978

he stated that "ultimately the discussion, kinds of facility and guidelines are simply irrelevant." In his view, human security may be threatened by "the biologic revolution." He notes tht just as the "nuclear reality" has led to the term "omnicide," and environmental pollution to "ecocide," biological research may lead to "genecide."

As noted in my Decision document (FEDERAL REGISTER,) July 28, 1978), NIH has been asked to provide a forum for dealing with social issues relatig to "genetic engineering." The concerns of this witness may be taken in the same context. My Decision notes that NIH has been addressing the policy questions involving the safety of this research, not the "potentential future application * * * to the altering of the genetic character of higher forms of life, including man * * *. In light of public concern, a study is warranted of the ethical, legal, and social implications of these techniques. The National Commission for Protection of Human Subjects of Biomedical and Behavioral Research considered, but was unable to initiate, a study * * *." Such a study might be considered by the Department's newly created Ethical Advisory Board. It could also be a key priority for the National Commission for the Protection of Human Subjects, which was reauthorized by the Congress before adjournment of this session.

APPENDIX II—FEDERAL INTERAGENCY ADVISORY COMMITTEE ON RECOMBINANT DNA RESEARCH, OCTOBER 1978

DEPARTMENT OF AGRICULTURE

Dr. James Nielson, Deputy Assistant Secretary for Conservation, Research, and Education, U.S. Department of Agriculture, Washington, D.C. 20250.

Charles F. Lewis, Ph. D. (Alt.), Staff Scientist, Plant and Entomological Sciences, National Program Staff, ARS, USDA, BARC-West, Beltsville, Maryland 20705.

Dr. Clarence O. Grogan (Alt.), Principal Agronomist, Conservation, Research, and Education, U.S. Department of Agriculture, Washington, D.C. 20250.

DEPARTMENT OF COMMERCE

Jordan J. Baruch, Sc. D., Assistant Secretary for Science and Technology, U.S. Department of Commerce, Washington, D.C. 20230.

DEPARTMENT OF DEFENSE

William R. Beisel, M.D., Scientific Adviser, U.S. Army Medical Research Institute of Infectious Diseases, Ft. Detrick, Frederick, Maryland 21701.

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Lowell T. Harmison, Ph. D., Science Adviser, Officer of Health Policy, Research, and Statistics, OASH, Parklawn Building, Room 17A-55, Rockville, Maryland 20857.

CENTER FOR DISEASE CONTROL

John H. Richardson, D.V.M., Director, Office of Biosafety, Center for Disease Control, Atlanta, Georgia 30333.

Anthony Robbins, M.D., Director, National Institute for Occupational Safety and Health, Parklawn Building, Room 8-05, Rockville, Maryland 20857.

FOOD AND DRUG ADMINISTRATION

Robert L. Elder, Sc. D., Deputy Associate Commissioner for Science, Food and Drug Administration, Parklawn Building, Room 14-57, Rockville, Maryland 20857.

Rosa M. Gryder, Ph. D. (Alt.), Staff Science Adviser, Office of Science, Food and Drug Administration, Parklawn Building, Room 7-83, Rockville, Maryland 20857.

John C. Petricciani, M.D., Deputy Director, Division of Pathology, Bureau of Biologics, FDA, NIH Building 29, Room 514, Bethesda, Maryland 20014.

DEPARTMENT OF ENERGY

James L. Liverman, Ph. D., Deputy Assistant Secretary for Environment, Department of Energy, Washington, D.C. 20545.

Charles E. Carter, M.D. (Alt.), Manager, Biomedical Programs, Office of Health and Environmental Research, Department of Energy, Washington, D.C. 20545.

Walter H. Weyzen, M.D. (Alt.), Manager, Human Health Studies Programs, Office of Health and Environmental Research, Department of Energy, Washington, D.C. 20545.

DEPARTMENT OF INTERIOR

Mariano Pimentel, M.D., Medical Director, Department of Interior, 18th and C Streets, NW., Room 7045, Washington, D.C. 20240.

DEPARTMENT OF JUSTICE

Mr. Anthony Liotta, Deputy Assistant Attorney General, Land and Natural Resources Division, Department of Justice, Washington, D.C. 20530.

DEPARTMENT OF LABOR

Eula Bingham, Ph. D., Assistant Secretary for Occupational Safety and Health, Department of Labor, Washington, D.C. 20210.

DEPARTMENT OF STATE

Mr. William J. Walsh III, Biomedical Research Liaison and Health Affairs Officer, Bureau of Oceans and International Environmental and Scientific Affairs, Department of State, Washington, D.C. 20520.

DEPARTMENT OF TRANSPORTATION

Mr. Douglas A. Crockett, Department of Transportation, Trans Point Building, Room 6405, 2100 Second Street SW., Washington, D.C. 20590.

ENVIRONMENTAL PROTECTION AGENCY

Thomas A. Murphy, Ph. D., Acting Deputy Assistant Administrator for Health and Ecological Effects, Environmental Protection Agency, 401 M Street, SW., Washington, D.C. 20460.

EXECUTIVE OFFICE OF THE PRESIDENT

Gilbert S. Omenn, M.D., Ph. D., Assistant Director for Human Resources, Office of Science and Technology Policy, Old Executive Office Building, Room 360, Washington, D.C. 20500.

Mrs. Carroll L. Bastian, Senior Staff Member for Environmental Health and Toxic Substances, Council on Environmental Quality, 722 Jackson Place, NW., Washington, D.C. 20006.

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION

David L. Winter, M.D., Director for Life Sciences, National Aeronautics and Space Administration, 400 Maryland Avenue SW., Room 5111, Washington, D.C. 20546.

NATIONAL SCIENCE FOUNDATION

Herman W. Lewis, Ph. D., Section Head of Cellular Biology, Division of Physiology, Cellular, and Molecular Biology, National Science Foundation, Washington, D.C. 20550.

Philip D. Harriman, Ph. D., Program Director of Genetic Biology, National Science Foundation, Washington, D.C. 20550.

NUCLEAR REGULATORY COMMISSION

Mr. Frank Swanberg, Jr., Chief, Health, and Environmental Research Branch, Nuclear Regulatory Commission, Washington, D.C. 20555.

U.S. ARMS CONTROL AND DISARMAMENT AGENCY

Robert Mikulak, Ph. D., Physical Science Officer, Multilateral Affairs/Advanced Technology, U.S. Arms Control and Disarmament Agency, Washington, D.C. 20451.

VETERANS' ADMINISTRATION

Jane S. Schultz, Ph. D., Chief, Program Review Division, Veterans' Administration Central Office, 810 Vermont Avenue, NW., Room 755, Washington, D.C. 20420.

CHAIRMAN OF THE COMMITTEE

Donald S. Fredrickson, M.D., Director, National Institutes of Health, Bethesda, Maryland 20014.

EXECUTIVE SECRETARY OF THE COMMITTEE

Joseph G. Perpich, M.D., J.D., Associate Director for Program Planning and Evaluation, National Institues of Health, Bethesda, Maryland 20014.

APPENDIX III

EXCHANGE OF LETTERS BETWEEN SENATORS AND SECRETARY CALIFANO

[Letter to Senator Kennedy attached; similar letters were sent to the five other Senators]

UNITED STATES SENATE,
Washington, D.C., June 1, 1978

Hon. JOSEPH A. CALIFANO, JR.,
Secretary of Health, Education and Welfare, Department of Health, Education and Welfare, Washington, D.C. 20201.

DEAR MR. SECRETARY: Since 1976 four committees of the House and Senate have held nine series of hearings to consider the issues relating to recombinant DNA research. These extended and thorough inquiries have shown that, with respect to the research they support and conduct, the National Institutes of Health have taken a properly cautious approach by prohibiting certain presumably hazardous experiments, requiring certification of the safety of host-vector systems, prescribing physical and biological containment measures for the con-

duct of permissible experiments, and providing for changes in these restrictions as further scientific evidence resolves the uncertainties about the health and environmental effects of using recombinant DNA techniques.

Evidence accumulated in the past year, rather than revealing any hazards associated with these experiments, points to a high level of safety in the use of the predominant host organism, the K-12 strain of *E. coli*. The NIH Recombinant DNA Molecule Program Advisory Committee has recommended changes in the Institute's research guidelines to reflect this evidence, and these recommendations are being considered by Director Fredrickson. Other hosts and vectors have received less scrutiny, and uncertainty remains about risks that may be associated with future applications of the technology. These uncertainties justify continuing to require certain precautions in recombinant DNA work.

However, the hearings have also underscored the need to correct deficiencies in the present system of regulation. Privately supported research activities are not subject to monitoring by NIH nor to sanctions for failure to comply with the guidelines. Application of the NIH standards by other Federal agencies is voluntary. As Director Fredrickson has stated on several occasions, it is doubtful this enforcement by the principal Federal sponsor of recombinant DNA research—NIH—is appropriate. Procedures for revising the standards and exempting certain experiments should be clarified. It is important to ensure the accountability of institutions and investigators, particularly if they are to assume greater responsibility for monitoring compliance. The Federal Government should anticipate commercial applications of recombinant DNA techniques and the concerns they are likely to raise.

In view of these developments and in view of the heavy legislative schedule of the Senate and the Human Resources Committee, we are writing to inquire whether the deficiencies in the present regulatory system can be remedied through executive action in the event final agreement on legislation is not possible. Specifically, it would seem possible to shift monitoring and enforcement responsibilities from NIH to a more appropriate agency within the Department of Health, Education, and Welfare. It would also seem possible to remedy the problems of accountability and of coverage in the process of revising the recombinant DNA guidelines. On the basis of the survey of existing statutory authorities conducted by the Committee on Commerce, Science and Transportation, there seems to be adequate authority to regulate the commercial application of products developed through recombinant DNA technology. There is, however, need for more effective coordination among Federal agencies in the implementation of these authorities.

In this regard, you expressed to Senator Stevenson in your letter of February 27, 1978, that the Food and Drug Administration "* * * could, under existing authority, require any firm seeking approval of a product which may be the end product of recombinant DNA research to certify to the Agency that it has complied with the NIH guidelines on recombinant DNA." You noted also that FDA has authority to inspect firms making such certification to assure compliance with the NIH guidelines. This statement is important because most, if not all, recombinant DNA research by the private sector is being conducted by pharmaceutical companies with the objective of developing products that would be marketed in accordance with FDA regulations. A decision by the Administration to use this existing authority would bring the large majority of privately funded recombinant DNA research activities under the NIH guidelines. Is the Administration prepared to use the authority cited in your February 27th letter?

Finally, it has been suggested that section 361 of the Public Health Service Act provides sufficient authority to promulgate regulations covering recombinant DNA research conducted by the private sector with non-Federal funds. Although you have expressed the view that specific legislative authority is preferable to using the authority of section 361, we are raising the issue again for three reasons: (1) The need for new legislation is less clear than it was one year ago when the initial bills were introduced, (2) the existing regulatory deficiencies relating to Federally-supported research can be remedied by executive action, and (3) the heavy legislative schedule may preclude action in this session of Congress. In view of these developments, it seems prudent to explore the willingness of the Executive Branch to use the authority of section 361 to cover privately-funded recombinant DNA research. In addition, we request that you solicit a legal opinion from the Department of Justice as to the use of section 361 in this manner.

There is an additional factor to consider. In the past, Congress has been reluctant to extend statutory control over a specific field of scientific investigation unless such authority was absolutely necessary to protect the public's health and safety. In view of the scientific evidence accumulated during the past year, it is not possible to reach this conclusion in the ease of recombinant DNA research. If the deficiencies discussed above could be corrected through executive action—by use of existing powers of FDA and/or the authority of section 361—there would be no reason to legislate new statutory controls.

In the event these executive actions were implemented, we would recommend that an appropriate group of experts and lay persons, such as the advisory committee to the NIH Director, continue to monitor the scientific evidence relating to the hypothetical risks of recombinant DNA research. If evidence indicating actual risks were to be developed, Congress could once again consider the need for legislation.

Since we are presently considering the legislative agenda for the balance of this session, we would appreciate your prompt response to this inquiry.

Sincerely,

EDWARD M. KENNEDY,
Chairman, Subcommittee on Health and Scientific Research.

JACOB K. JAVITS,
Ranking Minority Member, Committee on Human Resources.

GAYLORD NELSON,
Member, Committee on Human Resources.

ADLAI E. STEVENSON,
Chairman, Subcommittee on Science, Technology and Space.

HARRISON A. WILLIAMS, JR.,
Chairman, Committee on Human Resources.

RICHARD S. SCHWEIKER,
Ranking Minority Member, Subcommittee on Health and Scientific Research.

THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE,
Washington, D.C.. September 12, 1978.

Hon. EDWARD M. KENNEDY,
Chairman, Subcommittee on Health and Scientific Research, Committee on Human Resources, United States Senate, Washington, D.C. 20510

DEAR TED: Thank you for your letter in which you have raised a number of thoughtful questions concerning the need for legislation to regulate recombinant DNA research.

As you state in your letter, new scientific information, particularly on the safety of *E. coli* K-12 (the principal organism used in these experiments), indicates that extensive regulation in this research area may be unwarranted. Indeed, there is additional evidence that many recombinant DNA manipulations in the laboratory may be similar to events that occur in nature.

In view of these scientific developments, you raise the question as to whether legislation is necessary or whether existing statutory authority would be sufficient for purposes of regulation. You cite specifically the regulatory authority of the FDA and of the Public Health Service Act (Section 361).

The Department does not intend to invoke existing statutory authorities to regulate DNA activities at this time. If an emergency were to occur before passage of legislation, the Department could reconsider this position in order to take action on an interim basis. But, we continue to support legislation if it embodies the moderate approach of H.R. 11192. The virtue of such legislation is that it may include a number of specific provisions that permit useful flexibility in implementing regulations. Such provisions include:

- the promotion of uniform national standards,
- clear authority for the Secretary in relationship to other Federal laws,
- avoidance of normal administrative procedures for initial application of NIH Guidelines and waiver of the Administrative Procedures Act (APA) for issuance of administrative regulations, and authority for the Secretary to waive regulatory requirements for activities that pose no significant risk to health or the environment.

In recommending legislation, the Federal Interagency Committee on Recombinant DNA Research reviewed all existing statutory authority and found that none could provide for comprehensive regulation of these activities. The Interagency Committee noted that under Section 361 "there would presumably have to be a reasonable basis for concluding that the products of all re-

combinant DNA research cause or may cause human disease. Such a conclusion would undoubtedly be tenuous at best, and it is unlikely that resulting requirements could be effectively imposed and enforced."

Your letter suggested that we seek a legal opinion from the Department of Justice on the use of Section 361. Justice is represented in the Interagency Committee and has participated in the review and recommendations concerning existing statutory authorities, including Section 361.

The authorities of the Food and Drug Administration (FDA) were reviewed by the Committee; but inasmuch as recombinant DNA research has not yet reached the stage where it has yielded products to be regulated by FDA, it was agreed that FDA probably does not have authority to impose requirements on such research at present.

On July 28, the Department published proposed revisions to the Guidelines on recombinant DNA research for 60 days of comment. In addition, I have asked General Counsel Peter Libassi to serve as Chairman and Dr. Donald Fredrickson as Vice Chairman of a September 15 public hearing on these proposed revisions. Analysis of written and oral comments will proceed as quickly as possible, with final issuance of the revised Guidelines expected before the first of December.

A number of proposed changes in the Guidelines would permit, on a voluntary basis, registration of activities and NIH certification of new host-vector systems from the private sector. Protection would be provided for proprietary an patent information for these private sector activities. Registration of recombinant DNA projects, irrespective of source of funding, would be required of institutions receiving NIH support for recombinant DNA research. By these means, a national registry of all Federal and private sector activities may evolve.

The Interagency Committee has been an invaluable forum for developing coherent and coordinated policies through the representation of all the relevant research and regulatory agencies, and has served to ensure a commonality of standards. This Committee should continue to provide such oversight for the development of Federal policies and to ensure institutional compliance with the NIH Guidelines. Other advisory committees, both technical and public, must continue. The Recombinant DNA Advisory Committee will have a continuing role, and as you suggest in your letter, the public Advisory Committee to the Director, NIH, should continue to consider recommendations from the technical group.

The NIH and the Center for Disease Control (CDC) will continue to work closely as they have done over the past 18 months concerning safety aspects of the Guidelines. For example, NIH, in conjunction with CDC, has been developing mechanisms for assisting institutions in managing possible laboratory emergencies and for providing direct assistance when appropriate. Indeed, NIH and CDC are collaborating in a revision of the CDC Classification of Etiologic Agents on the Basis of Hazards—a classification that underpins some of the safety requirements of the Guidelines. Also, these agencies are reviewing packaging and shipping requirements relavant to recombinant DNA activities.

Close cooperation and consultation with the Food and Drug Administration and the Environmental Protection Agency will also be essential, since the regulatory authority of these agencies will come into play when recombinant DNA research inventions are ready for commercial development. The Occupational Safety and Health Administration will exercise its regulatory authority in the workplace.

We are pleased with the progress made in the absence of legislation and believe that invocation of existing authorities, however appropriate, would not contribute materially to our objectives. Only passage of legislation embodying the features cited here would, in our opinion, justify the change from a voluntary to a regulatory approach. Should the Senate choose to act, I would strongly urge adoption of an approach similar to H.R. 11192.

Sincerely,

JOSEPH A. CALIFANO, Jr.

[FR Doc. 78-35532 Filed 12-21-78; 8:45 am]